

UNIVERSITY OF EDINBURGH THESIS

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Degree: *Ch. M.*, Year: *1935*

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THE MORBID PHYSIOLOGY OF INTESTINAL OBSTRUCTION

with Special Reference

to

Low Obstruction

and to

Strangulation of the Bowel.

THESIS

submitted for the degree of Ch.M.(Edin.)

October, 1935

by

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INTRODUCTION.

The original work presented here is almost wholly experimental, but all experimental surgery must find birth in clinical observation, and no conclusions drawn from experiment are clinically applicable unless the disease in the experimental animal is constantly compared with the disease in man. A chapter has accordingly been devoted to the clinical varieties and features of intestinal obstruction, and a chapter to its morbid anatomy.

The main substance of the thesis is concerned with low intestinal obstruction and with strangulation of the bowel, but no consideration of these would be complete without an understanding of the chemical changes which occur in high intestinal obstruction, and an account of this condition is given in the fourth chapter. In chapter seventeen, presentation is made of a scheme of treatment based on recent experimental and clinical observations. The great majority of the measures suggested are generally accepted already as good surgical practice, but the statements in this chapter are advisedly general, since certain of the forms of treatment considered

are based on the conclusions drawn by a single observer, and have not yet been practically applied to man.

Acknowledgement must be made of the facilities afforded to the author by Professor D. P. D. Wilkie, in the Surgical Research Department in Edinburgh University, where this work was planned and commenced, and by Dr Evarts A. Graham, Director of the Department of Surgery, Washington University, St. Louis, Missouri, U.S.A., where the major part of the research was performed. The St. Louis experiments were carried out with the constant advice of Dr Robert Elman.

THE MORBID PHYSIOLOGY OF
ACUTE INTESTINAL OBSTRUCTION.

I. HISTORICAL CONSIDERATIONS.

In 1848 Benjamin Phillips⁽²³⁾ of Westminster Hospital, observed that "at this advanced period in the history of medicine, it might be reasonably supposed that a disease must either be very insignificant in its consequences, or of very uncommon occurrence, if it have escaped very ample, and, it may be, sufficient consideration: and no doubt the expectation would be usually realised. But there are diseases which are neither uncommon nor insignificant, and yet their history remains to be told: and of the number are obstructions of the bowels dependent on internal mechanical causes".

When these words were written little indeed was known of the causes of acute intestinal obstruction, and there was no clear picture of the symptoms or of the pathology of the diseased bowel. The ancients dismissed the disease usually in a sentence, though Celsus⁽⁸⁾ stressed the importance in prognosis of a

foul black vomit, and Aretaeus the Cappadocian recognised⁽¹⁾ that small intestine obstructions are more dangerous than those of the colon. In later Roman times operations were occasionally undertaken for the release of strangulated hernia, and a Martial epigram refers to such an operation ("Metius implicitas Alcon secat enterocelas")⁽¹⁹⁾. As early as the fourth century B.C., Praxagoras of Cos⁽²⁴⁾, one of the Asclepiadae, is said to have advised laparotomy for intussusception. In those days, however, the sufferers were thought to die simply of excessive pain⁽²⁾, and the cause of death in obstruction was not a problem for the early physician.

In the middle ages, and later to the early nineteenth century, the importance of the pain of acute obstruction was reflected in the title awarded the disease - "Miserere mei, the iliac passion"^{(13) (22)} - and the mediaeval and early modern observers, feverishly searching for a means of overcoming the mechanical obstruction, failed to consider why such an obstruction should have a fatal effect.^{(9) (16) (20)}

Already in 1700 the first certainly successful operation for "internal strangulation" was recorded by Bonetus⁽⁵⁾, and soon the mortality from operation

was low enough for surgical intervention to be seriously considered⁽¹²⁾ ⁽¹⁸⁾ as an alternative to the administration, no less heroic than operation, of such simples as lead shot⁽¹¹⁾ and metallic mercury⁽²¹⁾. The titles of the early monographs on acute obstruction are a sufficient indication of the contemporary knowledge of its pathology.

In the latter half of the nineteenth century, the growth of operative surgery and the increasing safety of laparotomy in the hands of Brinton⁽⁶⁾, Rokitansky, Bryant⁽⁷⁾, Fagge⁽¹⁴⁾, Treves⁽²⁵⁾ and many others,⁽³⁾ ⁽¹⁰⁾ led to an exact knowledge of the causes - bands, adhesions, intussusception, volvulus and the rest - of production of acute obstruction of the bowel, but still mention is rarely made of the reason why death should occur. Beveridge suggested⁽⁴⁾ that the most important pathological feature was the mechanical obstruction to the circulation of blood in the bowel; Fagge observed the extreme scantiness of urine in high obstruction but failed to deduce from that the importance of fluid loss: Bryant believed that death was due to inflammation of the distended gut.

This silence over the cause of death in

obstruction was broken by the voice of only one lonely inspired experimentalist, when Gaspard⁽¹⁵⁾ reported that the injection of extracts of putrid meat in experimental animals gave a symptom complex and a pathologic picture identical with those which follow the injection of the content of obstructed bowel. He observed even the congestion of the upper jejunum which ninety years later was to be such a constant sequel of the injection of Whipple's closed-loop toxin. Founder as he was of the experimental study of obstruction, and of the "toxic theory" of the disease, Gaspard remained a voice crying in the wilderness until Kocher⁽¹⁷⁾ more than half a century later commenced his experiments on acute obstruction, and opened one of the most important chapters of experimental medicine.

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II. THE MORBID ANATOMY OF ACUTE INTESTINAL OBSTRUCTION.

From a pathological viewpoint, it is necessary to adopt some simple classification of intestinal obstruction, and it is generally recognised now that there are four main varieties.⁽²⁶⁾

(1) In Simple Occlusion (further subdivided into high and low small intestine obstruction, and colonic obstruction), there is a mere mechanical blockage of the lumen, with no primary alteration in the circulation of the bowel. This variety is seen in its pure form in early cases of obturation by foreign bodies or gallstones, in compression by bands, adhesions, and tumour pressure from without, in congenital stenosis and in neoplastic stricture of the bowel itself.

(2) In Closed Loop Obstruction, a segment of bowel is completely isolated by double occlusion from the remainder of the intestinal tract. This in its ^{usual} ~~present~~ form is seen in obstructive appendicitis, when a concretion, a stricture, or a tumour closes the only exit from the organ. It is also seen in loops lying between multiple tuberculous, inflammatory or neoplastic strictures, & in loops doubly compressed

by multiple bands. The enterocyst or isolated remnant of the vitello intestinal duct is a sterile closed loop.

(3) Strangulation of the bowel is primarily an interference with the circulation of the bowel. Its pure form is best represented by mesenteric embolism and thrombosis, where there is no initial occlusion of the lumen. In volvulus, intussusception, and strangulated hernia, the venous return is impeded early, and overshadows in importance the obturation which accompanies it. Strangulation may be arterial or venous. The venous form is the more common, for a compressing agent will exercise its effect first on the low pressure veins. In embolism of a large mesenteric artery, a segment of bowel loses its blood supply, and may be momentarily white and anaemic, but the collateral circulation in the bowel is always liberal, and blood is soon poured by anastomosing vessels into the paralysed vascular bed of the anaemic bowel, and remains there stagnant. An intestinal infarct is almost always black. White infarction of the bowel is excessively rare, and occurs only in certain cases of sudden impact of an embolus in the superior mesenteric trunk.

(4) Paralytic or Adynamic Ileus has long been recognised as a special variety of acute obstruction. In this form, no organic lesion can be demonstrated and the stream of content is slowed and stopped as a result of a failure of peristaltic contraction. The loss of motive force is usually due, probably, to a reflex increase in sympathetic inhibition (whose stimulus may be an abdominal operation) or to the direct action of a poison (as sometimes in septicæmia) on the muscle or the intramural nerve-plexuses of the abdominal wall. It is convenient to include here also the rare condition of spastic ileus, where a tightly-contracted ring of circular muscle blocks the passage of bowel content.⁽¹³⁾ Since these obstructions of nervous origin differ from simple occlusion only in their method of production and in their difficulty of treatment, they will not be specially considered in this thesis, where we are concerned only with the effect on the organism of an obstruction already produced.

While this classification is a useful one, the types are not always clear-cut. In a simple occlusion or in a closed loop obstruction, as the upper bowel distends, the tension in the distended wall soon

exceeds the pressure in the intestinal veins, the circulation in the bowel wall is slowed, and the condition approaches one of strangulation. The cyanosed muscle, at first hyperactive, soon loses its motility, and even after relief of the obstruction, contractility may be slow in returning, and the patient after operation may be in a condition of paralytic obstruction.

Conversely[?] in strangulation, even if the lumen is not occluded when the vascular interruption occurs, the cyanosed bowel loses its motility and fails to contract, and the features of simple occlusion are added to the more serious features of strangulation.

In simple obstruction, as when a ligature is tied round the bowel, normal movement continues for a time in the gut below the obstruction,⁽⁷⁾ and absorption proceeds there too; the volume of content below the lesion decreases, the intra-intestinal pressure falls, the stimulus for contraction is lost, and peristalsis soon diminishes. Above the obstruction, the intestinal content lies stagnant and fermenting; there is no outlet for the gaseous fermentation products, the intra-intestinal pressure rises, absorption, at first accelerated temporarily by the rise in

pressure, soon diminishes and ceases, and mucus secretion is hastened.⁽²⁾ The intra-intestinal pressure thus rises in a steeper and steeper curve, and in response to the increased pressure, movements in the muscle of the obstructed segments become more rapid and more violent.⁽⁷⁾ Reverse peristalsis probably occurs in the obstructed bowel,^(3, 4) but to determine the direction of the contracting wave by direct observation is difficult, and it is probable that though the contents of the bowel are forced upwards, the movements in the wall have mainly a downward direction. If a rubber tube, closed at one end, is "milked" downwards towards the closed end, its contents will escape backwards by a flow in the opposite direction. Brinton indeed, on experimental grounds rejected the theory of reverse peristalsis entirely, and described in obstructed bowel, as in a syringe with a closed nozzle but an opening in the piston, a double current - a downward current peripherally, and an upward stream (towards the piston of the syringe) in the centre.⁽⁶⁾

As the intra-intestinal pressure rises, it soon exceeds the pressure of blood in the intestinal veins, venous drainage is lessened, and the blood stagnates

the portion from argument is by no means clear

in dilating vessels and capillaries. Oedema follows in the intestine walls, leucocytes migrate into the tissue spaces, the capillary walls burst and there is a perivascular extravasation of blood, first into and even through the mucosa, then into the muscularis, and finally in the subserous space and through the serosa to the peritoneal cavity. The anoxaemic epithelial and mucosal cells show at first cloudy swelling, and later complete necrosis. These changes are most marked at the antimesenteric border, where the blood supply is least liberal,⁽⁵⁾ but may involve the whole circumference, and oedema and perivascular haemorrhages are usually obvious in the mesentery also. The intestinal lymphatics are outlined by blood-stained content, the mesenteric glands are often swollen and oedematous, and the thoracic duct may contain blood-stained fluid.⁽¹⁶⁾ Ultimately thrombosis may occur in the intestinal veins,⁽¹⁾ but this final stage is usually preceded and prevented by earlier death.

After death, the bowel contains thick, dark brown or black fluid - partly digested food, bile, pancreatic and intestinal juices, mucus, epithelial cells, and blood. The lower loops show the greatest

pathological change - congestion, oedema, leucocyte infiltration, haemorrhages, microscopic necrosis of cells, antimesenteric ulceration, and even (in 20 per cent ⁽⁵⁾) patches of purple or green gangrene. These changes lessen as the distended bowel is followed proximally, till in the upper jejunum and duodenum there is only a diffuse reddening and oedema of the mucous coat, ^(23, 24, 25) from capillary distention. ⁽¹⁴⁾ The peritoneal cavity may contain yellow or light brown fluid in small amount, with a few leucocytes and red blood cells.

The changes in the wall of a closed loop are similar to those in a simple obstruction, but are more rapid in their development if infection is present (this is discussed more fully in a later chapter), less rapid if the content is sterile.

In strangulation, congestion, oedema and haemorrhages are almost immediate, and gangrene, though it may be confined to the antimesenteric border of the bowel, is invariably present before death.

Perforation of the bowel and peritonitis are rare in any form of obstruction, but least uncommon in certain malignant lesions of the colon.

The liver after death shows central necrosis of

its lobules, which in 11 per cent. may be as well marked as in fatal cases of septicaemia.^(8, 12, 14, 22) The sinusoidal spaces are dilated,^(11, 20, 21) and are rapidly invaded by anaerobic organisms after death.⁽⁸⁾ The liver fat increases, and the glycogen content falls.⁽¹⁹⁾ On the other hand, death may occur without any histological or naked eye evidence of liver damage.⁽⁹⁾

The pancreas often shows capillary dilatation, oedema, and vacuolation of cells.⁽¹⁷⁾ The kidney cells too may be swollen and vacuolated.⁽²¹⁾ The spleen is usually congested⁽¹¹⁾ and swollen,⁽²¹⁾ with follicular hyperplasia.⁽¹⁵⁾ The adrenal glands have been loosely described as presenting "characteristic changes."^(10, 18)

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III. CLINICAL FEATURES OF ACUTE
INTESTINAL OBSTRUCTION.*

The initial symptom in acute intestinal obstruction is pain, in the form of a colic whose spasms are synchronous with the more violent contractions of the distending bowel above the lesion. The higher the obstruction, the higher will be the point in the abdominal wall to which the pain is referred. When distention becomes considerable, it furnishes a background of dull discomfort for the sharp attacks of recurrent colic. The pain is the result of stimulation of sensory nerve-ends in the bowel wall, but whether this is due to direct compression of the nerve ends by the contracting wall, is not certain. No form of abdominal pain is more severe than that occasioned by an embolus lodging in a mesenteric artery, and it is possible that violent contraction on the one hand, and excessive distention on the other, cause sensory stimulation only in so far as they

* Since the symptoms and signs of acute obstruction are of enormous importance in any consideration of the cause of death in this condition, they will be considered in greater detail later. It is convenient, however, to have the salient features collected here in a special chapter.

produce a local anoxaemia of the nerve ends. It has been shown⁽¹⁾ in man, during the measurement of intra-intestinal pressure by a jejunostomy tube, that colicky pain occurs only with contractions which raise the pressure within the bowel to about 200 millimetres of water, and van Zwahlenberg⁽⁵⁾ has shown that at this pressure the capillary stream is markedly slowed. Spasm sufficient to cause pain is always sufficient to give local circulatory change in the bowel wall. Experimentally, spasm cannot be produced without local anaemia, and local anaemia of the bowel is always followed by spasm, so that it has never been shown which of these is the immediate cause of colic.

Soon after the occurrence of obstruction, there may be one bowel movement, or the passage of a little flatus, but after this, and usually without this indeed, there is no evacuation and no flatus so long as the intestine remains obstructed.

Vomiting is the rule, early and severe in high small intestine obstruction, late in low obstruction. Recently taken food is regurgitated first, then bile-stained fluid, and lastly the so-called "faecal vomiting" of the dangerously late case, when altered blood, bursting into the lumen through over-distended

capillaries and a broken mucosa, ascends to the stomach, to be augmented there by similar haemorrhages from the congested vessels of the gastric mucosa, and to be vomited.

Distention is greater in low obstruction than in high - a central ladder pattern in small intestine obstruction, a peripheral colonic outline when the large intestine is distended.⁽³⁾ Vigorous peristalsis may be observed through the abdominal wall.

The skin and mucous membranes are dry, the features drawn and haggard, the urine scanty in amount and of high specific gravity. These manifestations of dehydration and their significance are fully discussed in a later chapter.

The pulse rate rises in the later stages, and the blood pressure falls. The temperature is usually subnormal.

In strangulation, the onset is more sudden and painful than in simple obturation, the fall in blood pressure is rapid and, since there is at first an enormously increased activity in the congested muscle of the strangulated loop, the blood poured into the lumen from congested capillaries may pass rapidly down the still open lumen, and be evacuated, in cases of

embolism, thrombosis, or intussusception, where occlusion is not immediate. The clinical features of closed loop obstruction are of special interest, and are considered in detail later.

It may be said that the higher an obstruction, the more intense are the symptoms and the earlier is death. A patient with a complete occlusion below the ampulla of Vater (the lethal point of Draper-Maury) may die if untreated in 48 hours. A patient with complete obstruction of the lower colon may live for many days. Strangulation is much more fatal than a simple occlusion at the same level, and a long loop with its veins ligated and its arterial supply uninterrupted is the most fatal form of intestinal obstruction, and may cause death in a few hours.⁽⁴⁾

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IV. HIGH INTESTINAL OBSTRUCTION.

Of all the varieties of intestinal obstruction, high obstruction has most attracted the interest of the experimentalist, and the gradual elucidation of the many interlocked and, at first, apparently contradictory features of this condition remains one of the most important recent chapters in experimental medicine.

It is now recognised, as a result of the work of Haden and Orr,^(27, 41) Armour,⁽²⁾ Wilkie,^(80, 82) Draper-Maury,^(13, 63) Elman and Hartmann^(16, 18) and a host of others, that all the phenomena of high intestinal obstruction are dependent on the loss to the organism of water and of inorganic ions which, poured into stomach and duodenum in enormous quantities as digestive juice, fail to pass beyond a high obstruction to be reabsorbed, as they are in the absence of obstruction, by the intestine below.⁽⁸⁰⁾ The heavy and progressive loss of water leads to an increasing dehydration, whose degree can be measured clinically by the dryness of the patient's skin, by the increasing thirst, and by the diminution in the output of urine. The blood becomes increasingly concentrated; the erythrocyte count^(19, 44, 51, 73) and the haemoglobin content rise,

there is an increase in the blood viscosity,^(19, 30,31,51) a prolongation of the sedimentation rate,⁽³²⁾ and a reduction of the total plasma volume.⁽⁵⁸⁾

The accompanying loss of inorganic ions would if uncompensated lead to a lessened electrolytic content of the blood, and a fall does indeed occur in its chlorides,^(2, 10, 19, 20,25,26,28,34,35,36,48,50,52) its sodium^(21,26,50,60) and its potassium.⁽⁵⁰⁾ An attempt is made by the organism to maintain the chloride level by the complete retention of chlorides from the urine,^(2,34) and by a passage of chlorides from the tissue fluids⁽³³⁾ to the blood. These measures fail to keep pace with the loss of chloride in the digestive juices, yet even in the absence of chloride, the electrolytic content of the blood must be maintained and the lost chloride must therefore be replaced by some other salt. The only electrolyte on which the organism can draw to an almost unlimited degree is bicarbonate; as the chloride content of the blood falls, the bicarbonate content rises, and alkalaemia results.^(1,2,20,21,24,27,28,34,42,45) The hydrogen ion concentration of the blood is thus less important than, and in high obstruction is sacrificed to, the maintenance of the total electrolytic content at a

constant level.⁽⁴⁹⁾ That the alkalaemia of high obstruction is due to retention of bicarbonate to replace the lost blood chloride and not only to the loss of acid in the vomited gastric juice^(2,43) is clearly demonstrated by the continued rise in the alkali reserve of the blood even in the later stages of high obstruction, when all free acid has long disappeared from the vomitus.⁽²⁾

Co-incident and parallel with the fall in blood chloride is a rise in the non-protein nitrogen of the blood.^(2,3,6,8,9,17,19,26,28,34,35,42,54,61,62,69,72,76,78)

This increase in non-protein nitrogen is too great to be explained merely by the increased concentration of the blood by dehydration. The diminished output of urine is not responsible for urea retention, for the urea excreted even in the scanty twentyfour-hour urine of an animal or man in high obstruction may be greatly increased.^(39,42,77) This suggests that the raised blood urea may be due to increased cell destruction in the parched tissues:⁽⁴³⁾ perhaps the protein molecule, deprived of its water of hydration in the general dehydration, is broken down to give increased production of urea.⁽³⁾ The high blood urea, further, may be an attempt at maintaining the osmotic pressure

*Cl must be lost
as HCl in wall
of the latter
where does the
Na of the NaHCO₃
come from.*

of the plasma, replacing chloride to some extent, since urea is a non-electrolyte with one-half the osmotic pressure of the molecular equivalent of fully dissociated salts.⁽⁴⁹⁾ The elevation in the blood protein, not as yet explained, is probably also dependent on dehydration and hypochloraemia. It is not solely due to the increased concentration of the plasma, for the globulin rises, while the albumin falls.⁽²⁶⁾

All these phenomena, ultimately responsible for death in high intestinal obstruction thus depend primarily on the loss of water and sodium chloride in the digestive juices, and the most severe and rapidly fatal form of small intestine obstruction is obviously that in which all the gastric juice, all the pancreatic juice, all the bile, and the great bulk of duodenal secretion fail to be reabsorbed - that is when the obstruction is located directly below the entrance of the biliary and pancreatic ducts into the duodenum - the "lethal line" of Draper Maury.⁽⁶³⁾ The severity of an obstruction varies roughly as its distance above or below this point. The effects of a high intestinal obstruction are thus precisely the same as the effects of a complete duodenal fistula, and the blood

changes described above can be exactly duplicated by draining from an animal its digestive secretions. (11, 12, 17, 18, 20, 22, 23, 66, 70, 74)

A similar train of effects is seen if dehydration and hypochloraemia occur from any other cause - administration of potassium carbonate, (5) pilocarpine salivation, (13) apomorphine vomiting, (71) gastro-enteritis in babies (17) and (sometimes) serum sickness in man.

If the symptom-complex of high intestinal obstruction be due purely to loss of water and inorganic ions, then complete relief should follow the administration of saline solution, and it has been abundantly proved that such relief can be obtained. Wilkie (81) first observed the clinical value of saline administration in high obstruction, and a host of later workers have shown that in experimental high obstruction, dehydration can be avoided, the blood chloride level can be maintained, the non-protein nitrogen kept from rising, alkalaemia prevented and death almost indefinitely postponed, by giving adequate quantities of physiological saline solution either parenterally (19, 28, 42, 44, 48, 58, 75, 81) or into the small intestine below the obstruction (2, 37, 56, 53, 54, 64, 67, 68, 79) (provided the stomach be kept empty by lavage (42)). Salts other

than sodium chloride are ineffective, concentrated solutions are less efficacious than physiological saline⁽⁴⁵⁾ (water is necessary as well as salt), and glucose solution is useless.

In final proof of the importance of the digestive juices in high obstruction is the repeated observation that death can be delayed for several weeks in the experimental animal by preventing loss of bile and pancreatic juice - by transplanting below the obstruction the bile duct and pancreatic duct, or the segment of duodenum which receives them.^(15,57) Most long-lived of all is the animal who has the obstructed jejunum implanted high in the stomach, and has the lower stomach and whole duodenum excluded and drained into the ileum⁽⁵⁵⁾ - very little of the digestive juice of such an animal fails to be reabsorbed, and the high obstruction in the jejunum is then of little consequence. The rectal administration of bile in high obstruction, strongly advocated for a time,^(4,7,14,65) thus has some justification, though it owes all its effect purely to the water and salt in which the bile salts and pigments, themselves inert, are dissolved.

The "toxaemia" of high intestinal obstruction has thus been experimentally reduced beyond all possible

doubt, to a simple loss of water and inorganic ions in the digestive juices. It remains only to enquire to what extent experimental high intestinal obstruction resembles acute intestinal obstruction as we know it clinically. In all the experiments cited in this chapter, high obstruction refers to an obstruction in the lower duodenum, or uppermost jejunum. An obstruction at this level is rarely met with clinically, except in the cyclic vomiting which occasionally follows gastro-enterostomy and other operations on stomach or duodenum, and it is in such vomiting as this that saline administration has its most dramatic effect. The lower the level of obstruction, the less is the relief afforded by saline administration, and in acute obstruction of the ileum - by far the commonest clinical form of the disease - though digestive fluids are lost, great loss of fluid and sodium chloride is a late feature; saline therapy, though still valuable, does not avert death and, as will be seen, some other cause of death than dehydration and hypochloraemia must be sought.

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V. THE CAUSE OF DEATH IN LOW

INTESTINAL OBSTRUCTION.

(1) The Theory of Dehydration and Hypochloraemia.

The effects of high intestinal obstruction, as have been seen, are due primarily and simply to loss of the digestive juices, and the consequent dehydration and hypochloraemia.

In low intestinal obstruction - obstruction of the ileum - dehydration and hypochloraemia play a much less important part. There is little vomiting, the skin remains moist until a late stage, and the urine does not rapidly diminish in amount.⁽⁴⁾ Dehydration is slight⁽⁴⁾ as measured by percentage of haemoglobin, red blood cell count and blood viscosity, and the maximum reduction of blood chloride is only 30 per cent, ^(2,4,5) as compared with 50 per cent. chloride loss in high obstruction.⁽¹⁾ The chloride content of the various body tissues is not reduced,⁽⁸⁾ with the possible exception of the skin chloride. There is no great alteration in the alkali reserve⁽²⁷⁾ and at the moment of death, the non-protein nitrogen of the blood, though usually increased, is less so than in fatal cases of high obstruction.⁽⁷⁾ In experimental low

obstruction, intravenous administration of saline solution fails to prolong life^(3, 6) and short-circuiting of the digestive juices by implantation of the excluded duodenum below the obstruction is equally ineffective.⁽⁷⁾ The view therefore that dehydration, hypochloraemia, alkalaemia and azotaemia, responsible as they are for death in high obstruction, are equally important in low intestinal obstruction, is untenable.

(2) The Theory of Splanchnic Congestion.

It has been shown⁽¹¹⁾ that if the portal vein be ligated, the blood trapped in the congested vessels of the intestinal wall, and so lost to the general circulation, is sufficient to explain the consequent fall of blood pressure and ultimate death. In complete portal obstruction the animal bleeds to death into the distended vessels of its splanchnic circulation. In intestinal obstruction, the distended obstructed bowel is congested often to a severe degree, if the intra-intestinal pressure is raised to a point beyond the pressure of the blood in the veins of the gut wall, and it has been suggested^(10,12) that enough blood may be held up in the dilated intestinal capillaries to be a serious drain on the total blood volume.

This suggestion is capable of easy proof or

disproof by simple experiment.⁽⁹⁾

Experiments I - IX: Each of nine cats under ether anaesthesia had a silk ligature tied tightly around the ileum, eighteen inches above the ileo-caecal junction. Two fine seromuscular knots of silk were placed in the gut wall one foot above, and one foot below the point of obstruction to measure off respectively the lowest foot of obstructed bowel, and an equal adjacent loop of unobstructed bowel. In two of the cats the obstructing ligature broke or cut through and the animals recovered. The remaining animals died after periods of one to six days. In these, the two measured loops were excised after death, and their mucosal surfaces dried by the passage of a cotton pull-through. Only a drop or two of blood was lost from each loop during excision - from the vessels of the mesentery, and of the loop ends. The difference in weight between the measured unobstructed foot of bowel, and the lowest foot of obstructed bowel, was taken to represent the maximum possible surplus of blood in the congested wall of the latter - an obvious over-estimate, since some part of the increase in weight must be due not to blood but to cedema fluid. This difference varied from 0.23 to 2.5 gm. or,

expressed as a percentage of the blood volume of the animal (arbitrarily estimated as $7\frac{1}{2}$ per cent. of the body weight) from 0.11 to 1 per cent. of the blood volume. Since the lowest obstructed loop was in all cases the most congested, this figure multiplied by the number of feet in the length of the small intestine was taken to represent the maximal possible blood loss into the wall of the whole obstructed small intestine. This total loss varied from 0.6 to 5 per cent. of the estimated blood volume - a loss comparable with only a trivial external haemorrhage. In these animals there had been no obvious loss of blood by diapedesis or haemorrhage through the walls of the intestinal vessels into the lumen.

No. of Expt.	Weight of Cat	Estimated Blood Vol.	Gain in Weight of lowest obstructed loop	Gain in Weight expressed as percentage of B.V.	Maximum loss into whole small intestine
I.	1500 gm.	112 cc.	0.9 gm.	0.8%	$3\frac{1}{2}\%$
II.	2000	150	1.2	0.8%	3.2%
III.	1500	113	1.1	1%	4%
IV.	3300	248	2.5	1%	5%
V.	2300	Obstruction incomplete.			
VI.	2700	Ligature cut through. Cat recovered.			
VII.	2900	218	0.2	0.1%	0.6%
VIII.	2400	180	1.7	1%	5.5%
IX.	2000	150	0.2	0.13%	1%

From these experiments, the possibility that an animal can die from bleeding into the vessels of a simply obstructed bowel can be rejected, and the Theory of Splanchnic Congestion is disproven.

(3) The Nervous Theory, or the Theory of Reflex Shock.

It has been contended⁽¹³⁾ that death in low obstruction is due to the central passage of nervous impulses from the distended bowel, but until recently, there has been little proof of any such reflex depression. Herrin and Meek, however, have found⁽¹⁴⁾ that balloon distention of a Thiry Vella fistula in the dog (that is, balloon distention of an excluded and unobstructed loop of bowel draining externally on the surface) will give death in eight days with diminution of blood chlorides, and elevation of the non-protein nitrogen. This distention was borne indefinitely, however, without loss of chlorides and with no other ill effect if the distended loop was first denervated. Herrin and Meek make no attempt to explain this strange reflex loss of chlorides, and their work has not been confirmed. It has been shown already that death in low obstruction is not generally associated with loss of chlorides, yet the possible importance of afferent

*Significant
symp. are
sufficiently
low chlorides*

nervous impulses from a distended gut must be remembered. Taylor, Welch and Harrison⁽¹⁵⁾ have also found balloon distention of a Thiry Vella loop to be fatal in the dog, but they were not successful in prolonging life by denervation of the distended loop. These effects of intestinal distention will be more fully discussed later (page 101).

(4) The Toxic Theories.

A. Bacterial Toxins in Obstructed Bowel.

Bacteria probably swarm more thickly in the normal intestine than in any other sphere of non-pathological nature, and this is true of all animals with the exception of infant mammals,^(38,49) the Arctic fauna,⁽³²⁾ and hibernating animals toward the end of Winter.^(17,30) Bacteria have therefore been blamed for the invasion of the blood-stream through the devitalised distended bowel^(16,20,26) but it is now accepted as the result of repeated careful experiment^(22,28,29,31,33) that no bacteraemia can be demonstrated in intestinal obstruction in man or in most experimental animals, although organisms can often be isolated from the blood soon after death.^(27,28) In the obstructed dog, a mild bacteraemia can sometimes be demonstrated during

life, but in that animal *B. coli*, *B. mesentericus*, and the enterococcus are often to be found in the blood even in health.^(19, 48)

There is no doubt of course that organisms multiply enormously in the lumen of the bowel above an obstruction⁽³³⁾ and a great predominance of proteolytic forms develops. Strong support was therefore given for a time to the view that these swarming organisms, while not entering the bloodstream themselves, might elaborate in the bowel a toxin to pass into the blood and give not a bacteraemia but a toxaemia - the toxaemia of intestinal obstruction. Williams^(46,47) pointed out that there was little to distinguish between the signs of the toxaemia of intestinal obstruction and the signs of *Bacillus Welchii* toxaemia - in both there is a rapid pulse, cyanosis (sometimes), general icterus (sometimes), restlessness, a pathologically acute consciousness, and after death a pronounced haemolytic staining of the great vessels. He demonstrated experimentally also that in obstructed dogs, just as clinically in man, the *Bacillus Welchii*, normally present only in the lower ileum, rises progressively in the alimentary canal until it ultimately appears in the stomach content and vomitus.

Struck by this apparent similarity between the two conditions, Williams proceeded to apply the administration of B. Welchii anti-serum in the treatment of acute intestinal obstruction, as a preliminary and as a sequel to operation.^(46,47) His results in a long series were dramatic, demonstrating a mortality of only 9.3% as compared with a control series in the same hospital, in which the mortality was 24.8%. As a result of Williams' findings, and of the findings of numerous French authors before him,^(25,36,44,45) who had found the antiserum valuable apparently in the treatment of acute appendicitis, an enormous amount of work was done along the same lines. While a few reported qualified success in the treatment of acute obstruction in man⁽²¹⁾ and in the experimental animals,^(24,34) no one obtained Williams' dramatic results, and a vast majority^(18,35,37,40,41,42,43) found that it made no difference to animals whether B. Welchii antiserum was given or withheld. It was shown further⁽³⁹⁾ that the antiserum gave an animal no protection against the injection of the content of an obstructed bowel, and that it was impossible by repeated injection of that content to confer on an animal any immunity to B. Welchii toxin. It is indeed the

simplest argument of all against the B. Welchii theory, that one attack of acute intestinal obstruction does nothing to mitigate the "toxaemia" of a second. If there is a "toxin of acute obstruction" it cannot for this reason, be a specific antigen.

In all respects therefore, the B. Welchii theory is now generally disregarded, and no proof has been offered that the toxin of any micro-organism is responsible for death in clinical or experimental cases of acute intestinal obstruction.

B. Chemical Toxins in Obstructed Bowel.

The foul stagnant content of a completely obstructed bowel loop has long suggested (51,53,67,92,93) that the symptoms of low obstruction are due to absorption of some part of that content. The high non-protein nitrogen of the blood was at first adduced as evidence of toxaemia, but this reaches its highest level in high obstructions, where its cause has been explained (p.24), and it can no longer be used in any argument concerning low obstruction since in this variety the non-protein nitrogen is rarely elevated to a dangerous degree. The view that the blood chlorides were low in obstruction because the chloride ion was used to neutralise a hypothetical toxin⁽⁷⁶⁾

was rapidly discarded by its promoters. There is no doubt, however, that obstructed bowel does contain highly toxic elements,^(52,68,72) notably the products of protein decomposition - proteoses, peptones, kyrines, histamine (which represents also, probably, "Vaughan's toxic fraction"), phenols, mercaptan, as well as choline and neurine from lecithin, glucosamine derivatives of mucin, and oxycholesterol. The "sepsin" of Faust⁽⁷¹⁾ and the neurine-choline theory⁽⁸³⁾ received no general support, and have long been discarded. The intestinal toxins which have been most investigated have been the proteoses and histamine.

Whipple first isolated from high closed intestinal loops, a substance with the chemical properties of a proteose^(98,99,102) which when injected in other animals^(91,102) produced a fall in blood pressure, dilatation of splanchnic vessels, fall in temperature, rise in pulse rate, increased concentration of blood, congestion of duodenal mucosa, and death in a few hours. This work was repeatedly confirmed.^(54,55,57,58,59,60,62,64,69,78,84,89,90)

There was never any demonstration, however, of the proteose in the blood of an animal or man suffering from intestinal obstruction; Immunity to the

toxin could not be established.^(57,63,65,66) No ill effects followed the introduction of closed loop fluid into normal bowel.^(62,97,100) Whipple himself⁽¹⁰⁰⁾ believed the toxin to be elaborated by the duodenal mucosa, and in the absence of obstruction to be neutralised by the contents of the lower bowel, but his results were disputed.⁽⁹⁶⁾

Histamine too has been long recognised as a normal chemical constituent of the intestinal content of man and dog,⁽⁷⁷⁾ but it is either not absorbed by normal intestinal mucosa or else, if absorbed, it is rapidly detoxicated and disappears from the blood.^(73,95) Its absorption from obstructed bowel has never been demonstrated.

There is no doubt therefore, that obstructed bowel contains toxic elements - notably proteoses and amines - but the contents of healthy unobstructed bowel are almost, if not quite, equally toxic.^(56,61,62,70,74,77,79,80,81,82,88,94) The main difficulty has been to demonstrate the absorption of these toxic elements into the blood when intestinal obstruction is present. It has been repeatedly suggested that a substance not capable of passing the normal intestinal mucosa, perhaps passes more easily a mucosa devitalised

and even ulcerated, as it may be in obstruction.
The effect of distention upon intestinal absorption
must therefore be considered.

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VI. LOW INTESTINAL OBSTRUCTION (contd.)

The Relation of Intra Intestinal Pressure to Intestinal Absorption.

There is no need here to dwell on the capacity of the intestinal mucosa to absorb, as it does in health, fatty acids, glycerol, glucose and the various electrolytes and amino-acids. Let it only be said that the absorption rate of diffusible substances probably increases with an increase in intra-intestinal pressure to a certain level - between 37 and 55 mm. of mercury in the case of the dog^(1,18) - but beyond that pressure level the intestinal circulation slows, the absorption rate falls again, and absorption of sodium chloride, for example, ceases altogether at an intra-intestinal pressure of about 65 mm. of mercury.⁽¹⁾ At the last pressure the flow in the veins of the intestinal wall has ceased⁽²⁰⁾ and no further absorption is possible. This intra-intestinal pressure is often exceeded in acute obstruction.

Apart from these normally absorbed substances, however, the possibility of absorption by the normal intestine of unaltered protein, is an important one,⁽¹⁷⁾ since certain of the bacterial toxins are of this

chemical constitution. The most complex colloidal poisons are of course harmless when taken by mouth (snake venom, ricin,³ abrin), but in certain circumstances unaltered protein may pass the barrier of the intestinal mucosa - normal human infants can be temporarily immunised to egg-white, sheep serum and amandin given by mouth;⁽²⁾ marasmic infants show a special ability for the absorption of unaltered protein, and can be sensitised even to cow's milk taken by mouth.⁽²⁾ Animals can be readily sensitised to horse-serum and other unaltered proteins if these are introduced into a doubly ligated loop of intestine.⁽⁹⁾ Gentian violet, which has a high molecular weight, will pass from the lumen of a loop of bowel to stain gauze applied to the peritoneal surface.⁽⁴⁾ Mice will absorb tetanus toxin given by mouth, and develop symptoms of tetanus, if large doses are given, liberally mixed with bile.⁽¹²⁾ In certain circumstances therefore, substances not normally absorbed by the bowel, may pass from intestine to blood.

Is an increased intra-intestinal pressure one of the circumstances which permit absorption of these substances not normally absorbed? The question has been widely investigated, and it is generally agreed



that no such increased absorption occurs, though Stone and Firor⁽¹⁶⁾ showed that the toxic contents of a closed intestinal loop suspended in Ringer in vitro, passed through into the surrounding fluid when the loop was alternately distended and collapsed. The cramps and convulsions of strychnine poisoning are delayed by injecting strychnine into a distended closed loop of bowel longer than they are when a similar strychnine injection is made into a normal loop.^(3,11,12,13) The symptoms may indeed be postponed in their entirety until the obstruction is released, when they come on with lightning rapidity. The absorption of salt solution, grape sugar, haemolysin, congo-red, fluorescein and carmine is lessened by raising the intra-intestinal pressure.⁽¹⁴⁾ Trypan blue, vital red, congo red, cloth red, congo blue - all colloidal substances - if introduced into the lumen of a distended bowel loop, do not appear in the vessels of the wall,⁽¹⁵⁾ and colloidal silver does not pass from the lumen of a distended loop to its lymphatics.⁽¹⁵⁾ The absorption of phenol-phthalein too, as estimated by its appearance in the urine, is slowed by increasing the intra-intestinal pressure.⁽⁵⁾ The reduced absorption of substances from the lumen of a distended

bowel loop is easily explained, of course, by the state of the circulation in the wall. Zwahlenberg⁽²⁰⁾ studied the circulation in obstructed bowel by direct microscopy, inserting an electric light bulb in one end of a living loop, and inflating the loop from the other end - at a pressure of 60 mm. of mercury the circulation was arrested in many small veins; at 130 mm. all circulation ceased; gut kept at 80 mm. for one hour became enormously congested, and exudation of fluid occurred. Similar observations were made by Morton⁽¹³⁾ (who X-rayed distended gut after injecting barium mixture into the aorta), by Gatch⁽⁸⁾ (who canalised the veins of a distended loop and measured the volume return per minute) and by Dragstedt⁽⁶⁾ (who repeated Zwahlenberg's work).

Although, however, it is certain that no absorption into the blood is possible of any toxin from the lumen of a grossly distended bowel loop, this in itself is no proof that a toxæmia does not occur. In low obstruction, the bowel loops are not all equally and progressively distended throughout the course of the disease. A low, grossly-distended loop may, by contraction, force a part of its content upward to a less distended loop, where the circulation

is not yet entirely stagnant, and where absorption can still occur, and when the low loop relaxes again, there is probably a moment of lessened pressure before it re-distends, permitting the veins to empty, and the blood in them, heavily charged with the diffusible content of the bowel, and with the products of metabolism from the anoxaemic tissues of the bowel wall, to return to the general circulation.⁽¹³⁾ If this interpretation of events is correct, then the most intense period of toxæmia should occur not during a low obstruction, but immediately after its release, and there is some clinical evidence that this is true. Dramatic death may often follow the sudden release of an intestinal obstruction^(10,7) - so frequently, indeed, that the gradual decompression of cases of low obstruction is increasingly popular.^(7,18) The experimental aspects of the sudden release of intestinal obstruction are studied later (p. 67). Here let us consider the evidence in favour of toxæmia as a cause of the symptoms of low obstruction.

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VII. EVIDENCE FOR AND AGAINST THE PRESENCE
OF A TOXIN IN THE BLOOD IN ACUTE LOW
INTESTINAL OBSTRUCTION.

It is impossible from clinical evidence alone to decide whether toxaemia is present or not in low intestinal obstruction. Fever may be present or absent. The pulse rate is usually increased, but often not until death is approaching. Vomiting is usually slight. Headache is unusual, and delirium is exceptional - the mind is usually clear almost until death. Skin eruptions are almost never observed. Death is often sudden, unexpected and dramatic.

The obvious method (not necessarily a logical method) of proving or disproving the presence of a toxaemia in intestinal obstruction, is to subject an animal to low intestinal obstruction and observe whether the injection of its blood thereafter will give symptoms of poisoning in an unobstructed animal. The general symptoms of low intestinal obstruction are more specific in the dog than they are in man - rapid pulse, muscular tremors, hind-leg spasticity and ataxia, prostration, and death in a few days - without, usually, fever or vomiting.

Scholefield⁽²²⁾ found that the portal serum of three obstructed dogs, if kept on ice for twenty-four hours, was fatal to mice, while the systemic blood serum from the same obstructed animals, and the portal serum of healthy animals, was innocuous. By the injection of 200 cc. of blood from the mesenteric vein of the closed intestinal loop of a single dog just before death, Sugito⁽²⁶⁾ killed two other dogs in twenty-four hours, but these results he could not repeat. Cole and Elman,⁽³⁾ using portal blood from twenty-eight dogs before and after simple obstruction and closed loop obstruction, and injecting it into mice, found very little difference of toxicity in the specimens obtained after the production of obstruction, but what little statistical difference there was, lay in the direction of increased toxicity in these. Gurewitsch⁽¹²⁾ demonstrated in blood from obstructed animals a depressor property giving, in animals of the same species, vaso-dilatation and a fall in blood pressure. Nemilov,⁽¹⁸⁾ by anastomosing the circulation of a healthy dog with that of a dog in acute obstruction, obtained a fall in the blood pressure of the former after one or two hours: Sauerbruch,⁽²¹⁾ much earlier, sewing together the abdominal muscles of two rabbits, one of which was later obstructed, found that both rabbits

died, but the obstructed one died twenty-four hours earlier than its partner, so that this evidence is hardly conclusive.

This short, slender summary indicates how unconvincing is the positive evidence in favour of a "toxæmia of intestinal obstruction", and an army of other investigators^(5,15,19,28,29) has been unable to demonstrate by injection experiments any increased toxicity in the blood of an animal after establishment of intestinal obstruction.

It has been shown^(3,25) that the passage of dyes and of colloidal silver into the thoracic duct is little affected by raising the intra-intestinal pressure, but attempts have been made to demonstrate the presence in experimental obstruction of toxin in the lymph from the thoracic duct. While such lymph certainly has been shown to contain at times an unusual amount of clotted blood⁽²³⁾ and even sometimes to have toxic properties on injection,⁽²⁾ these toxic properties are probably only present in infected lymph (infection of the thoracic duct may occur in acute obstruction)⁽²⁰⁾ and they are usually impossible to demonstrate.⁽¹⁶⁾

Experiments to alleviate the symptoms of acute experimental obstruction by drainage of the thoracic duct⁽⁴⁾

have been inconclusive.

The possibility of passage of poisonous content through the obstructed intestinal wall, and of its absorption by the peritoneum has also been widely investigated. It has been seen that in vitro, toxic material will pass from the lumen through the wall of an isolated closed bowel loop to the fluid in which that loop is suspended.⁽²⁵⁾ Perhaps similarly in obstruction a toxin may pass through the anoxaemic and sometimes partially devitalised bowel wall, to the peritoneal cavity to be absorbed, and Eisberg⁽⁸⁾ found that a completely exteriorised intestinal loop could be isolated and closed off without symptoms, while a closed loop laid subcutaneously in the abdominal wall had the same fatal result as an intra-peritoneal closed loop. Esau^(10,11) similarly found closed loops fatal when laid subcutaneously. Chénut's experiment⁽²⁾ with a subcutaneously-placed closed loop is inconclusive, since in his animal a fistula developed, the loop draining to the exterior and remaining collapsed. Dragstedt, however,⁽⁶⁾ transferred a closed intestinal loop from one dog to the peritoneal cavity of another, preserving the original blood supply. Synephrin, pilocarpine, ephedrine, and

sodium nitrite introduced into the loop had no effect on the second dog; nicotine poisoning certainly occurred in the second dog when nicotine was placed within the transplanted loop, but only after the death of the first (donor) dog and of the grafted loop. This demonstrates (as Buchbinder⁽¹⁾ proved earlier but less neatly) that peritoneal absorption of the material from an obstructed loop can occur only after that loop is dead and gangrenous. Nemilov⁽¹⁷⁾ found that the total fluid from the peritoneal cavities of several obstructed dogs had no effect on the blood pressure of a healthy animal. A closed bowel loop was extra-peritonealised by South and Hardt⁽²⁴⁾ but the usual "toxaemia" followed.

To investigate the importance of peritoneal absorption in closed loop obstruction, an attempt was made in Experiments 105 to 110 to exclude a closed loop from the peritoneal cavity, while leaving its blood supply intact. The loop having been isolated and its ends invaginated, it was enclosed in a rubber balloon whose neck was stitched by silk to the mesentery of the closed loop, and surrounded carefully by omentum, injury or compression of the vessels being avoided and the lumen being reconstituted. In several cases,

leakage occurred at the neck of the balloon, and these were discarded. In the six animals reported in Experiments 105 to 110, the balloon remained air-tight. In these, though no leakage occurred from balloon to peritoneal cavity, death occurred in less than twenty-four hours in every case, in a shorter time, that is, than if no attempt had been made to exclude the loop from the peritoneal cavity. In four of these animals death occurred before devitalisation was obvious in the closed loop. In the other two animals the loop in the balloon was cyanosed beyond the point of viability. These experiments show that death may occur in closed loop obstruction even though peritoneal absorption is prevented.

Injection experiments would appear on the surface to prove that no toxæmia occurs in low intestinal obstruction. The most superficial examination of the experiments at once demonstrates that as evidence of the absence of toxæmia they are hopelessly inadequate. Consider an animal dying of a minimum lethal dose of strychnine, of tetanus toxin, or of any other poison. By injecting a few cubic centimetres, or even a larger portion, of the blood of that dying animal into the veins of a healthy animal, would you expect severe

*Don't stop for
no stop
Don't stop*

symptoms (and symptoms must be severe to be observed in the experimental animal) of poisoning to develop? You have injected only a small fraction of the minimum lethal dose. The same holds true of any toxin that may be present in intestinal obstruction. Even the whole blood volume of a moribund animal will contain only a fraction of the minimum lethal dose if the toxin is present in the other tissues of the body as well as in the blood, and in no case has an amount approaching the whole blood volume of an animal dying of acute obstruction been tested for toxicity. In spite, therefore, of the number of experiments that have been performed, it remains an open question whether or not death in low acute intestinal obstruction is due to toxæmia.

If a toxin does pass from the lumen, or from the tissue spaces of the bowel wall, to the blood in the intestinal capillaries, it necessarily follows that the blood richest in that toxin is the stagnant anoxæmic blood in the congested vessels of a distended intestinal loop. But during actual distention of any distended loop there is, if the intra-intestinal pressure is sufficiently high within the loop, a complete arrest of circulation in the intestine wall, and it is

needless to expect to demonstrate, during actual distention, any toxin in the general circulation. One would expect the most profitable blood to examine for toxicity would be that leaving the mesenteric veins of a bowel loop immediately after release of distention. There is indeed some evidence that rapid release of obstruction will give a fall of blood pressure in an obstructed animal or man. Heusser and Schar⁽¹³⁾ and Elman⁽⁹⁾ have reported cases of sudden unexplained death following release of simple intestinal occlusions: Læwen⁽¹⁴⁾ obtained a marked fall in blood pressure in a dog when he "stripped" with his fingers a bowel loop obstructed for twenty-four hours; Wangensteen⁽²⁷⁾ found a similar fall in blood pressure when he released in animals temporary venous strangulation of the bowel, but not when he relieved a simple venous obstruction of kidney or spleen. A series of experiments was therefore planned to determine whether or not release of an obstruction of the bowel has any effect on the blood pressure. These experiments are considered in the succeeding chapter.

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VIII. EXPERIMENTS TO SHOW THE EFFECT ON
THE BLOOD PRESSURE OF SUDDEN RELEASE
OF INTESTINAL DISTENTION.

Experiments 41 to 55. In these experiments, temporary distention of the intestine was induced in the dog by placing one ligature tightly round the duodenum just above the ligament of Treitz, and a second ligature around the distal ileum; the whole small intestine thus isolated as a closed loop* was then distended by air until obviously cyanosed, and returned to the abdomen.

In the earlier experiments, sensory impulses from the distended bowel (which themselves have sometimes an effect, not yet determined, on the blood pressure) were interrupted by division of the plexus of nerves accompanying the superior mesenteric vessels, but this was obviously an inexact and incomplete method, and the same end was better reached in the later experiments by previous excision of the sympathetic chain and vagi. The denervation was done in two stages, with a month's

* It might be argued that a closed loop even of this length is not comparable with a clinical case of small intestine obstruction. This question is fully discussed on page .

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interval between; the distention experiment was performed one month after the second stage of the denervation. At each stage, with the use of intra-tracheal positive-pressure anaesthesia, the pleura on one side of the chest was opened by two incisions, in the 4th and 8th intercostal spaces respectively, the sympathetic trunk removed from the third thoracic ganglion to the diaphragm, the homolateral vagus resected immediately above the diaphragm, and the lumbar sympathetic chain removed extraperitoneally through a third (lumbar) incision.

After the intestinal distention had been present for a varying period of time, the visceral nerves having previously been interrupted in this way, the animals were again anaesthetised (by chloralose or intra-tracheal ether), a manometer cannula tied in one common carotid artery, the abdomen opened and the intestinal distention released suddenly by numerous punctures. In certain of the animals, the opposite carotid artery was ligated and both vago-sympathetic trunks excised in the neck to exclude the pressor and depressor cardiac reflexes, and ensure a maximum alteration in blood pressure.

In the intact animal and in the animal denervated

in the manner described, the blood pressure varies as the product of the cardiac output and the peripheral resistance. In experiments described here, the tonus of the skeletal muscles under intra-tracheal insufflation (which affects venous return to the heart) and the intrathoracic pressure (which stabilises soon after laparotomy if the exposed viscera are not handled) remain constant: the animal's position remains unchanged and the effect of gravity can be ignored: of the factors influencing the cardiac output, the available blood volume (which alters with the venous return from the cyanosed bowel) and the capillary tone thus remain the only variables.

The peripheral resistance depends in this case on the blood viscosity (which can be considered constant throughout the experiment unless altered by delay in the vessels of the cyanosed bowel) and on the state of the arterioles.

Arterial tonus is influenced through the vasomotor centre by -

- (1) The Higher Centres. These are out of action in the anaesthetised animal.
- (2) Carbon dioxide tension and H ion concentration of the blood. These are constant throughout the short duration of the experiments.

- (3) Oxygen lack and anaemia of the brain.
These are prevented by intratracheal insufflation.
- (4) Afferent influences from the cardio-aortic area and sinus caroticus. These are excluded by bilateral extirpation of the cervical vago-sympathetic, and ligation of the carotid arteries.
- (5) Afferent stimuli from other parts of the body. All stimuli are avoided in the experiments except those occasioned by the decompression of the bowel, and this has been previously denervated.
- (6) The ~~pressor~~ or depressor action of blood-borne substances on the vasomotor centre, or on the nerves and muscles of the arterioles. This is the factor under study.

In short, the blood pressure in the denervated animal will vary only with changes in the venous return from the deflated bowel, and with the effect of pressor or depressor substances returning in the intestinal blood when the distention is released.

The immediate effect of raising the intra-intestinal pressure to the point of cyanosis is a variable one, and depends on the nature of the bowel's reaction to the increased pressure within it. In certain cases the bowel contracts vigorously and pales, there is increased return of venous blood to the heart, and the compressed intestinal capillaries

*See distribution of the factor by the
the same substance*

offer increased resistance to the entrance of arterial blood (Fig. 1).

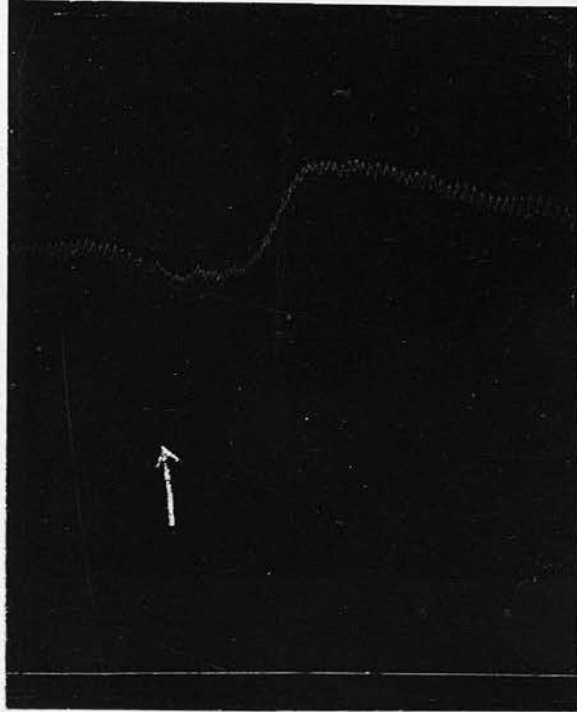


Fig. 1. Experiment 35. Blood Pressure of dog.
At arrow, intra-intestinal pressure raised to
100 mm. of mercury. Bowel contracts and pales:
B.P. rises from 98 to 146.

This rise in blood pressure is a transient one. If the high level of intra-intestinal pressure is maintained, the distended bowel, after five to fifteen minutes, relaxes, and its colour turns to bluish-purple. With the new colour change of congestion, the blood pressure falls below the original level. Venous congestion now in the bowel has reduced the volume of blood returning to the heart, and the open capillaries of the relaxed intestine, by permitting the easy entrance of arterial blood, reduce the peripheral resistance of the arterial tree.

In other animals, both in cats and dogs, the bowel does not react violently to the increased pressure within it, but remains flaccid, and rapidly enters a state of profound venous congestion. In these animals the blood pressure falls as soon as intestinal distention is induced, and there is no preliminary rise in blood pressure.

This reaction to an increase in intra-intestinal pressure obtained in seven animals (Experiments 38 to 44). (Fig. 2)

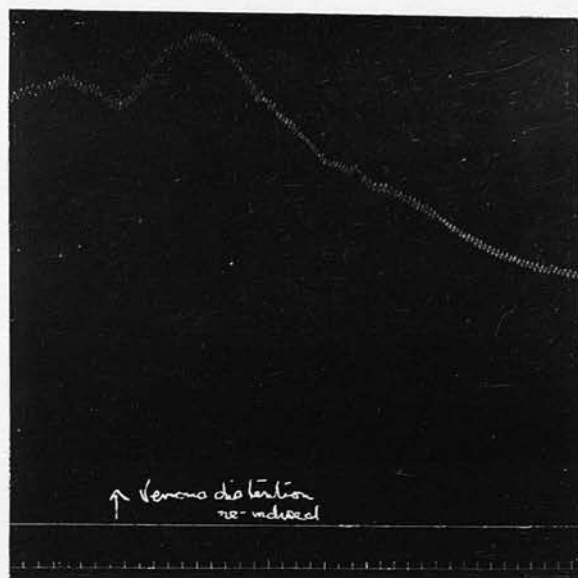


Fig. 2. Experiment 44. Blood Pressure of cat.
 Distention of bowel to 90 mm. of mercury.
 Transient pallor, then cyanosis, and fall of
 B.P. from 166 to 102.

The effect upon the blood pressure of suddenly reducing an intra-intestinal pressure sufficient to produce cyanosis of the bowel wall is a variable one, and depends upon the period of time over which the distention has been maintained. The results of such sudden deflation can be arranged in three groups.

(1) If an intra-intestinal pressure sufficient to cause cyanosis of the bowel wall is maintained for a period of seven or eight hours or less, the bowel

regains its healthy pallor, and the blood pressure rises, as a result no doubt of the increased return of venous blood to the right heart. This pressor effect on release of a shortlived intestinal distention was observed in eight animals (Experiments 41 to 48) (Figs. 3, 3A, 4 and 5).

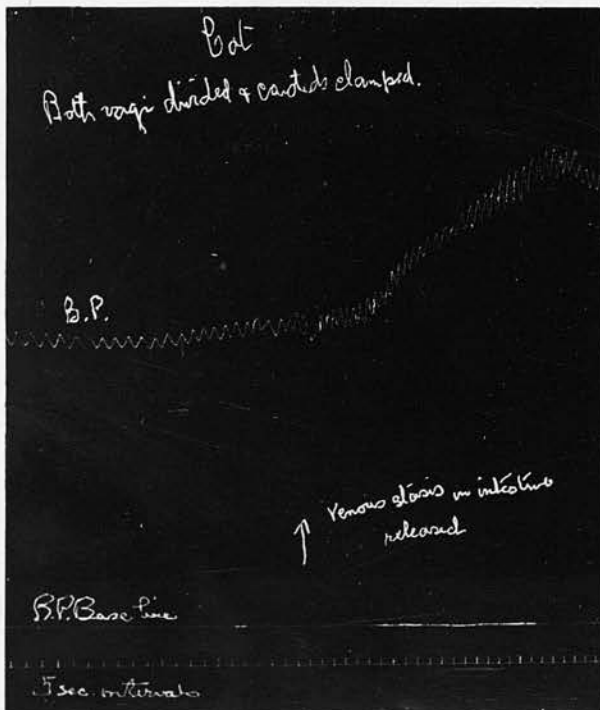


Fig. 3. Experiment 42.

B. P. of cat. At arrow, intestine deflated after five minutes distention at 80 mm. Hg. Cyanosis disappears. Blood pressure rises from 134 to 184.

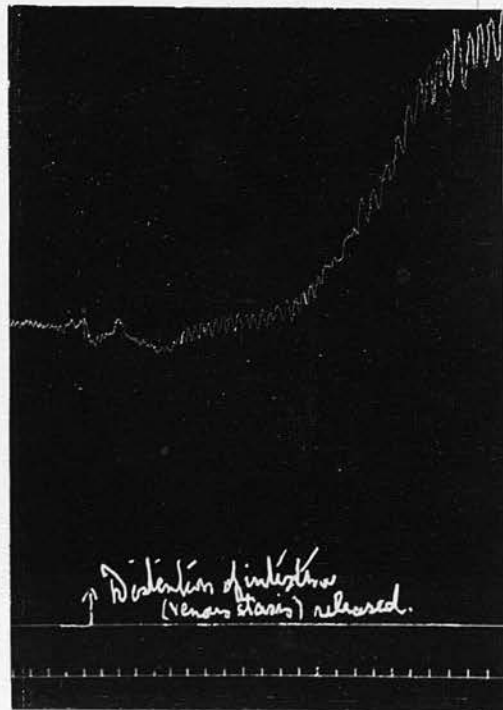


Fig. 3A. Experiment 48.

B. P. of cat. At arrow, intestine deflated after five hours at 80 mm. of Hg. Cyanosis disappears. B.P. rises from 116 to 184.

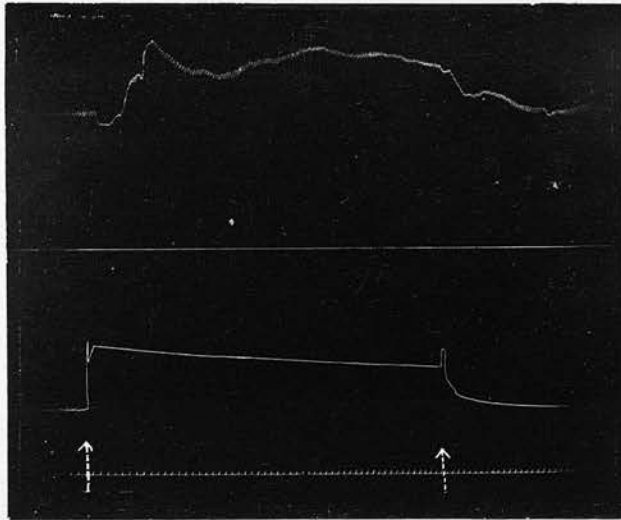


Fig. 4. Experiment 45. Dog. B.P.: (i) At first arrow, denervated intestine deflated after four hours at 100 mm. Hg. B.P. rises from 96 to 124. (ii) At second arrow, re-inflation: fall in B.P.

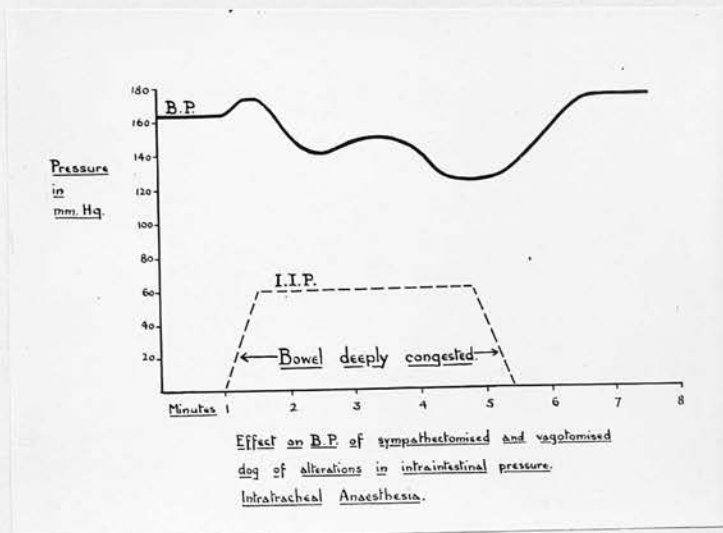


Fig. 5. Experiment 41.

The results in these experiments should be compared with Fig. 6, which shows a similar change in the

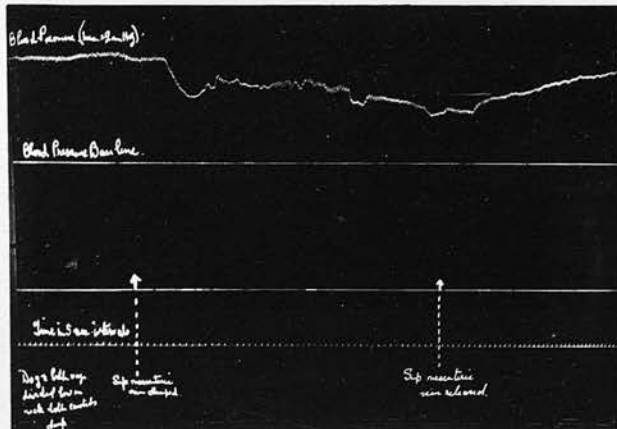


Fig. 6. Experiment 56. (i) Mesenteric vein clamped: (ii) clamps removed.

blood pressure, effected by clamping and unclamping the superior mesenteric vein. In both cases the effective factor is the alteration in the volume of blood returning to the right heart.

(2) If a similar intra-intestinal pressure, sufficient to cause cyanosis of the bowel wall is maintained for a period of more than six or eight, but less than seventeen or twenty hours, release of the distention, while still followed by disappearance of cyanosis in the bowel and resumption of a healthy

colour, is associated, not with the expected rise in blood pressure (though the volume of blood returning to the right heart is again increased) but by a fall in pressure. This depressor effect of release of an intestinal distention of medium duration was obtained in five animals (Experiments 49 to 53) (Figs. 7, 8, 9, 10, 11) and in one of these (50) the deflation was followed by a fall of pressure to 24 mm., and by death after only seven minutes.

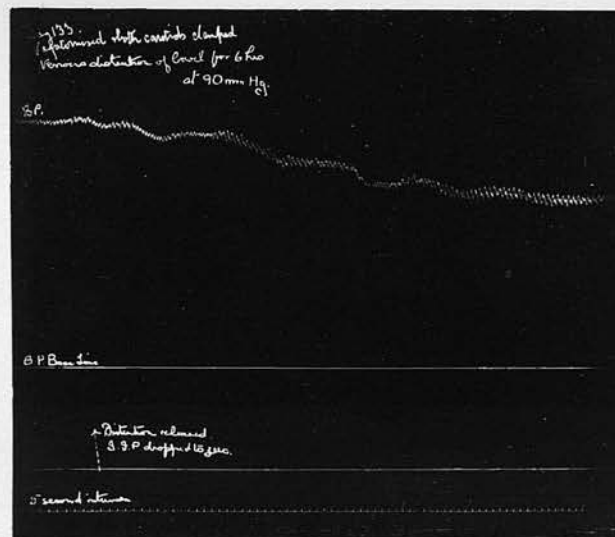


Fig. 7. Experiment 49. B. P. of dog.
Denervated intestine deflated after six
hours distention at 90 mm. Hg.: bowel
pales: B. P. falls.



Fig. 8. Experiment 53. Intact dog. B. P.
Deflation of intestine after twelve hours
distention at 80 mm. Hg.: bowel pales:
B. P. falls.

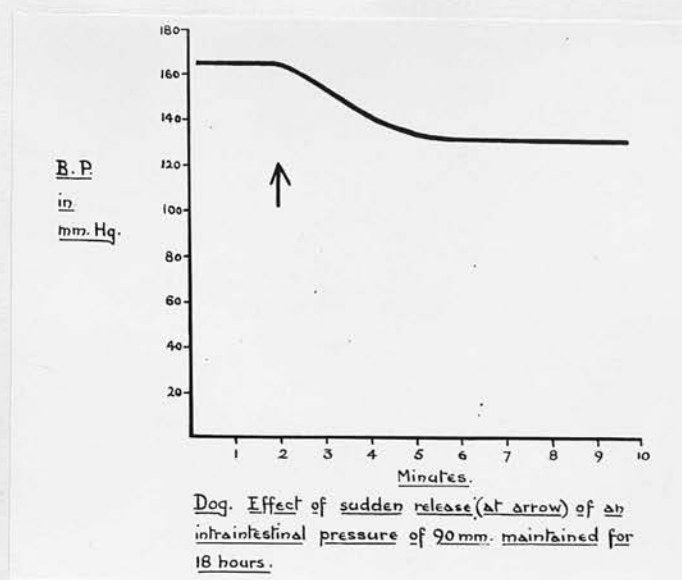


Fig. 9. Experiment 51.

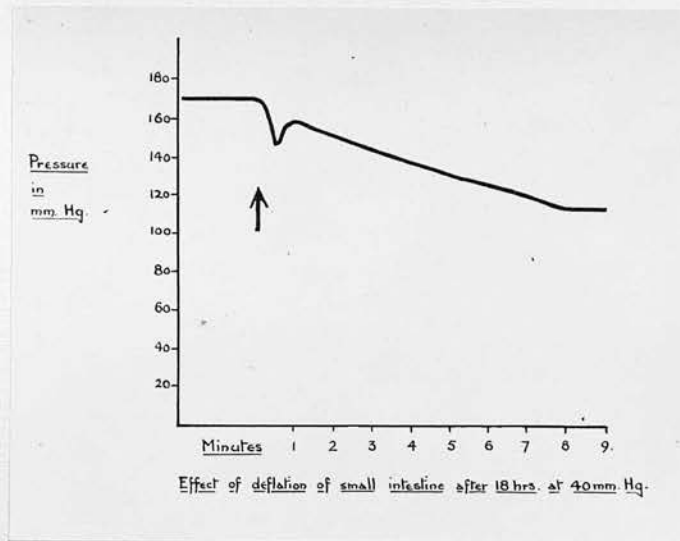


Fig. 10. Experiment 52.

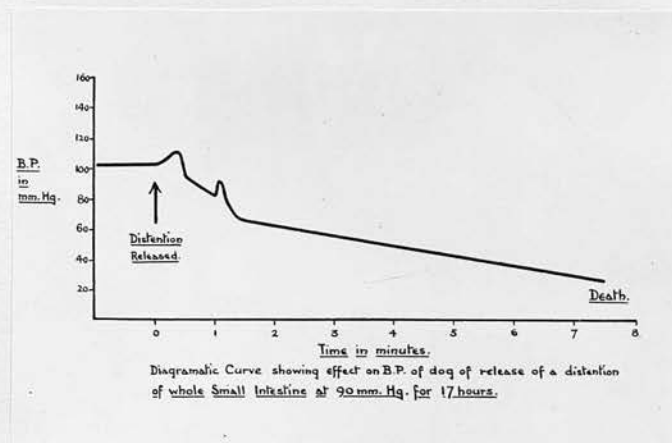


Fig. 11. Experiment 50.

The depressor effect obtained both in intact animals and in animals denervated in the manner described

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above, but in the intact animal (53) the depressor effect was not marked, being damped probably by the vago-pressor reflex in this case. This series strongly suggests that if blood is dammed up in the vessels of a distended intestine for an "incubation period" of 6-8 hours, it becomes endowed with depressor properties which it proceeds to exercise after its return, on deflation of the bowel, to the general circulation. In the animals denervated as has been described, there are no afferent paths remaining for a depressor reflex to follow: the volume of returning blood is increased and not diminished: the depression can only occur by general vaso-dilatation at the instigation of a blood-borne chemical substance.

(3) In two animals (54 and 55), whose intestines were distended to a degree of cyanosis for seventeen and twenty-one hours respectively, the bowel when deflated failed to resume its normal pallor, and thrombosis was obvious in its veins. Deflation in these gave no alteration in blood pressure - no blood passed from the intestine to augment the circulating volume on one hand, or to carry a depressor substance to the general circulation on the other.

The conclusions arrived at in these experiments can be briefly summarised thus:-

- (1) Inflation of the bowel to the point of cyanosis gives a fall in blood pressure, unless
- (2) Inflation elicits powerful contraction of the bowel, when temporary anaemia and a rise in blood pressure may precede the depressor cyanosis.
- (3) Deflation of a bowel which has been distended to the point of cyanosis for less than six or eight hours is followed by a rise in blood pressure: the blood returning now by intestinal, mesenteric and portal veins augments the circulating volume.
- (4) If distention with cyanosis is maintained for more than six or eight hours its release will be followed by a fall in blood pressure, even though the intestinal congestion subsides. This strongly suggests the passage of a depressor substance from lumen or tissue spaces of the anoxaemic gut to the blood in its congested veins, and the activity of that depressor, not during distention but after deflation of the engorged loop, when its blood is thrown back into the general circulation.
- (5) If distention with cyanosis is maintained for more than seventeen or eighteen hours, its release is followed by no change in blood pressure - thrombosis in the intestinal veins prevents any depressor substance from leaving the bowel wall. The problem is now not one of simple intestinal occlusion but one of strangulation.

TABLE Summarising Results of Experiments to Demonstrate the Time Factor in the Effect on the Blood Pressure of the Release of Intestinal Distention.

Expt. No.	Intra Intestinal Pressure Induced	Animal	Afferent Paths from Heart Interrupted	Afferent Paths from Gut Interrupted	Duration of Distention	Change in Bowel Circulation (Colour)	Alteration in B.P.	Explanation
41	62	Dog	Yes	No	5 Minutes	Return from cyanosis to normal	+28	Increased return of venous blood to Heart
42	80	Cat	Yes	No	5 Minutes	"	+50	
43	90	Dog	Yes	Yes	2 Minutes	"	+30	
44	90	Cat	Yes	Yes	5 Minutes	"	+102	
45	100	Dog	Yes	Yes	4 Hours	"	+28	
46	120	Dog	Yes	Yes	8 Hours	"	+44	
47	90	Dog	Yes	Yes	7 Hours	"	+22	
48	80	Cat	Yes	Yes	5 Hours	"	+68	
56	Release of ligation of superior mesenteric vein of dog					"	+24	
49	90	Dog	Yes	Yes	6 Hours	Return from cyanosis to normal	-55	Return of depressor substance in blood from intestine
50	90	Dog	Yes	Yes	17 Hours	"	-78 (death)	
51	90	Dog	Yes	Yes	18 Hours	"	-32	
52	40	Dog	Yes	Yes	12 Hours	"	-56	
53	80	Dog	No	No	12 Hours	"	-23	
54	90	Dog	Yes	Yes	21 Hours	Remained cyanosed	No change	Thrombosis in bowel veins
55	90	Dog	Yes	Yes	17 Hours	"	"	

IX. THE DEPRESSOR PROPERTIES OF PORTAL
BLOOD COLLECTED AFTER RELEASE OF AN
INTESTINAL DISTENTION OF TWELVE
HOURS DURATION.

The experiments in Chapter VIII are so suggestive of the return, in certain conditions, of some blood borne depressor substance in the portal blood after release of an obstruction, that an attempt was made to investigate the depressor effect of portal blood by a series of injection experiments. Since it appeared that the release of intestinal distention was followed by a fall in blood pressure only if the bowel had been distended for more than six or eight, and less than twenty-one hours, it was decided to test the portal blood of a dog for depressor properties upon release of a twelve hours' inflation - this inflation period, based on the results tabulated on the previous page, seemed to ensure the presence of the hypothetical depressor in the blood of the intestinal capillary bed, while falling well short of the period necessary for the supervention of thrombosis in the intestinal veins.

In Experiments 58 to 63 seven dogs were used. The whole small intestine was isolated by double

ligature as a closed loop, and distended by air to a pressure of 70 or 80 mm. of mercury - to a pressure, that is, sufficient to cause venous engorgement in the bowel wall. The distended loop was then returned to the abdomen and left undisturbed for twelve hours. At the end of this period the abdomen was again opened with sterile precautions, a cannula tied in the portal vein, and the distention rapidly released by multiple punctures of the bowel wall. The portal blood was then collected in a citrate flask as the bowel collapsed. Shaking of the citrated blood was avoided (agitation endows normal blood with depressor properties).⁽¹⁾ The citrated blood was kept on ice and its effect on the blood pressure of a second dog was determined by intravenous injection of the citrated blood, and of the plasma from it.

*? citrated blood
alone
H. Cantel*

The yield of portal blood from two of the dogs in this series was small. In these two the intestine failed to regain its normal colour on relief of the distention, and thrombosis had obviously occurred in the intestinal veins. Neither the portal blood nor the portal plasma from the animals gave a fall of blood pressure when injected in other dogs (Experiments 57 and 58).

2/6

In the remaining five dogs the intestine rapidly regained its normal colour on release of the distention, and from each of them 200 to 250 cc. of citrated portal blood was collected.

The specimen from one of these dogs failed to show any depressor properties (59).

The portal plasma and the portal blood from the remaining four dogs, however (60 to 63), when injected intravenously in doses of 15 cc. gave a marked fall in blood pressure in the recipient etherised dog (Figs. 12 and 13), and in one case (63) (Fig. 13) a noticeable fall in pressure followed the injection of only 3 cc. of portal plasma.



Fig. 12. Experiment 60. Effect on B.P. of dog of 5 cc. portal blood collected from dog after release of twelve hour intestinal distention.

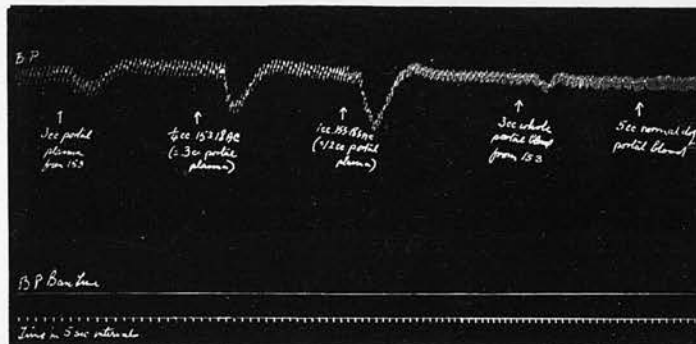


Fig. 13. Dog. B.P. I.V. injection of
 (i) 3 cc. portal plasma collected after
 release of twelve-hour distention:
 (ii) 1/4 cc. protein free filtrate of
 same plasma: (iii) 1 cc. protein free
 filtrate: (iv) 5 cc. portal blood of
 normal dog.

The portal plasma and citrated portal blood were drawn from four normal dogs as controls. In no case was the intravenous injection into other dogs of 15 to 30 cc. of these control specimens followed by a fall in blood pressure (Fig. 14).

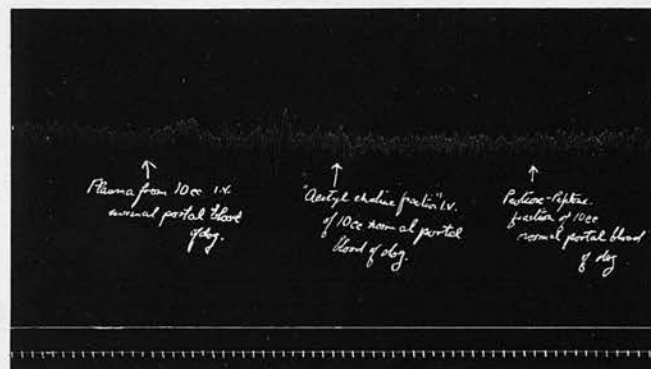


Fig. 14. Experiments 64 to 67. I.V. injection of (i) plasma, (ii) protein-free filtrate, (iii) proteose-peptone fraction of 10 cc. normal dog portal blood.

From these experiments, the conclusion must be drawn that a depressor substance can be isolated from portal blood after release of an intestinal distention, if that distention has been sufficient to cause cyanosis, and has been maintained long enough to allow the depressor to collect in the stagnant blood in the bowel wall, but not long enough to cause thrombosis in the bowel veins.

REFERENCE.

- (1) Phemister, D.B. and Hardy, J. Journ. Physiol., 1927, LXIV, 155.

X. THE CHEMICAL PROPERTIES OF THE DEPRES-
SOR SUBSTANCE PRESENT IN THE PORTAL
BLOOD OF THE DOG AFTER RELIEF
OF INTESTINAL DISTENTION.

By fractional precipitation with various saturations of ammonium sulphate, the englobulins, globulins and albumins were separated from the portal plasma of known depressor effect, collected from the four dogs mentioned above (Experiments 60 to 63). The eu-globulins were precipitated after the addition to the original active plasma of ammonium sulphate to a concentration of one third saturation; the globulins by one-half saturation, the albumins by full saturation with the same salt.

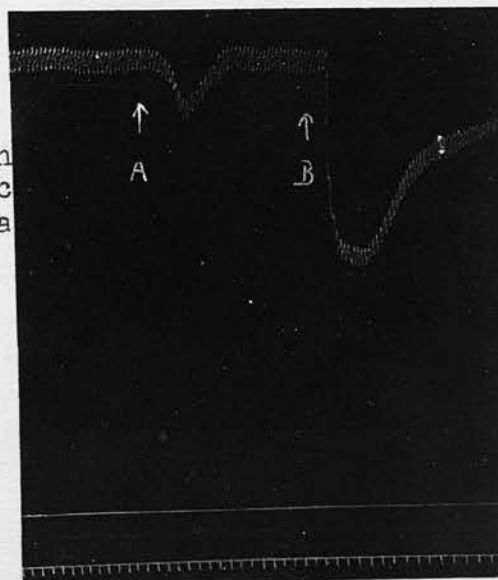
Dissolved in physiological saline and freed from ammonium sulphate by dialysis, none of these fractions exercised any depressor effect on the blood pressure of the etherised dog (Experiments 68 to 84).

Dialysis against water of the depressor-containing blood after full saturation with ammonium sulphate, and removal of the globulins and albumins by successive filtration, gave a clear solution presumed to contain any proteose or peptone from the portal blood of the

obstructed dogs. This fraction too had no depressor properties on intravenous injection, except in one instance, where inadequate dialysis was shown to have left a residuum of ammonium sulphate - itself a powerful depressor.

A protein free filtrate of portal plasma of known depressor effect was obtained by addition to the plasma of trichloroacetic acid to a concentration of 7.5 per cent. filtration, and extraction of the filtrate several times with ether. Each of the protein free filtrates of the four specimens of portal blood, described already as having a depressor effect, gave a definite fall of blood pressure in the etherised dog when injected intravenously in doses corresponding to as little as 6 cc. of the original plasma (14 cc. of the depressor portal blood) (Figs. 15 & 16) (Experiments 84 to 87).

Fig. 15. Experiment 84.
I.V. injection of protein free filtrate of (i) 6 cc (ii) 15 cc. portal plasma of dog after relief of twelve-hours distention.



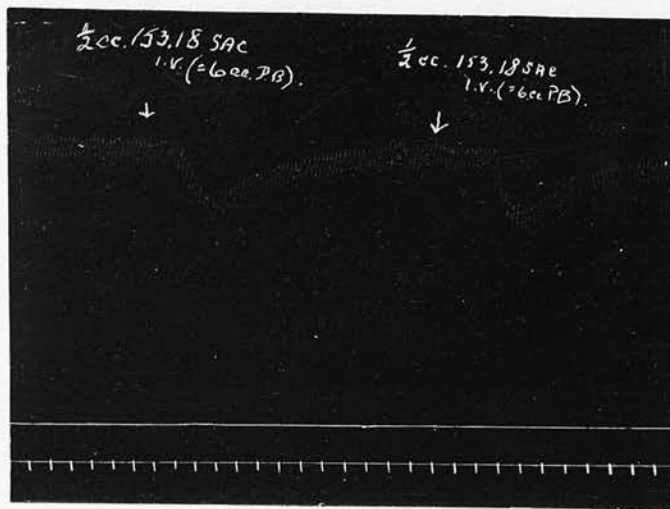


Fig. 16. Experiment 86. Same as 15, but doses here equivalent to 6 cc. portal blood in each case.

Similar doses of the protein-free filtrates from the portal blood of normal unobstructed dogs had no depressor effect on the blood pressure of the etherised dog (Experiment 88) (see Fig. 14).

The depressor activity of these protein-free filtrates of portal plasma from dogs after the relief of intestinal distention, persisted after neutral boiling and after acid hydrolysis (Fig. 17) (Experiments 89 & 90), but disappeared after alkaline hydrolysis (Experiment 91). Nitrite deamination

Fig. 17. Dog. B. P.
Deaminised filtrate of
6 cc. active portal
blood.



did not reduce the depressor activity of the active extract (Fig. 17) (Experiment 92).

When to an animal extract alcohol is added to a concentration of 80 per cent., and the alcoholic solution filtered, the histamine content is precipitated from the filtrate usually by the addition of three volumes of acetone. When the protein-free filtrate of the active portal plasma was treated in this way, the resultant precipitate failed to show any depressor activity towards the blood pressure of the etherised dog, when injected intravenously in

doses corresponding to 15 cc. of the original portal blood (Experiment 93).

The filtrate did not give the Pauly reaction for histamine (94).

XI. BIOLOGICAL ACTIVITY OF THE PROTEIN-
FREE FILTRATE OF PORTAL BLOOD DRAWN
FROM A DOG AFTER RELEASE OF
INTESTINAL DISTENTION.

The depressor effect of the extract on the blood pressure of the etherised dog has been fully described above. A similar depressor effect was obtained on the blood pressure of the etherised rabbit (Experiments 95 to 98), which is insensitive to histamine, and this effect on the rabbit was not abolished by previous atropinisation (Experiment 99) as is the depressor effect of acetyl choline. The filtrate had no effect on rabbit intestine (101), rectus abdominis of frog (104) or on eserinated leech muscle (102), which contract under the influence of acetylcholine, and no effect on the virgin guinea-pig uterus (100) which is stimulated by histamine. The jejunum of the cat, sensitive to histamine, remained unaffected by the filtrate (103).

Comparison of the Protein-Free Filtrate from Portal
Blood of Dog after Release of Intestinal Distention,
with the Depressors present in Tissue Extracts.

Since the depressor substance in the filtrate is

not precipitated from alcoholic solution by acetone, and does not give the Pauly reaction: since it has a depressor effect on the blood pressure of the etherised rabbit, and since it fails to stimulate virgin guinea-pig uterus or isolated cat jejunum, it can be assumed that this depressor is not histamine.⁽¹⁾

The stability of the depressor to acid hydrolysis and its resistance to deamination serve to distinguish it from adenosine.⁽²⁾

The filtrate resembles acetyl choline in its instability to alkaline hydrolysis, and in its depressor effect on the blood pressure of the etherised rabbit, but it has not the characteristic acetyl choline effect on rabbit intestine, on eserinated leech muscle, or on the rectus abdominis of the frog.⁽⁴⁾

The depressor substance closely resembles the "Substance P" of von Euler and Gaddum⁽³⁾ in its instability to alkaline hydrolysis, its resistance to acid hydrolysis and deamination, and its depressor effect on the blood pressure of the atropinised rabbit: the filtrate differed from "Substance P" only in its failure to stimulate isolated rabbit intestine.

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- (2) Dale, H.H. Bull. Johns. Hopk. Hosp., 1933, LIII, 323.
- (3) von Euler and Gaddam. Journ. Physiol., 1931, LII, 74.
- (4) Reisser, O. Arch. f. Exp. Pathol. u. Pharmak., 1921, XCI, 342.

XII. LOW INTESTINAL OBSTRUCTION.CONCLUSIONS.

If intestinal distention in the dog be maintained at a sufficient level to cause venous stasis in the bowel wall, and if that distention be suddenly relieved after more than six or seven hours, but before the occurrence of thrombosis in the intestinal veins, the blood pressure of the animal will tend to fall, and the portal plasma from that dog, withdrawn immediately after release of the intestinal distention, will in the majority of cases give a fall in the blood pressure of a healthy dog, if injected intravenously.

This depressor effect appears to be due to the presence in the portal plasma of a diffusible depressor substance which has not been exactly identified, but which in its biological activity and chemical properties resembles the "Substance P" of Euler and Gaddam more closely than it resembles the other known depressors of tissue extracts.

No attempt has been made here to determine whether the depressor substance has its origin in the lumen of the bowel, or in the bowel wall, nor is it possible definitely to blame the depressor substance, present

in portal blood after relief of intestinal distention, for the "toxaemia" present in the actual course of intestinal obstruction.

In a low obstruction, however, there is no reason for believing that any given loop of bowel remains equally distended and equally congested throughout the course of the disease. A bowel loop, distended and cyanosed at one moment, may by active contraction drive out the blood from its veins, and force its contents upwards to a higher loop, allowing a momentary re-establishment of circulation. At such a moment, that loop resembles on a small scale the long closed loop of our dogs, whose collapse gave such a dramatic fall in blood pressure. At such a moment, a depressor substance from the gut wall or lumen, which during cyanosis has diffused into the blood in the engorged vessels of the intestinal wall, can return with that blood now to the portal vein.

Since a sufficiently distended bowel loop has its circulation completely arrested, and since such a loop is incapable of absorption while it remains distended, the conception of the "toxaemia" of acute obstruction as a continuous stream of toxin from obstructed bowel to blood is untenable. The

conception of the "toxaemia" as a series of jets of depressor-containing blood, from the various congested loops, as the circulation is momentarily re-established in them at alternating intervals, is compatible with our previous knowledge of the morbid physiology of the obstructed bowel, and with the experimental phenomena presented in this thesis.

The collection of actively depressor portal blood in the actual course of a simple intestinal occlusion would be possible only if the momentary re-establishment of venous drainage from a distended loop could be anticipated.

XIII. CLOSED LOOP OBSTRUCTION.*

In the experiments described in the preceding chapters, a constant intestinal pressure in the obstructed small intestine was maintained by the isolation of the whole small bowel as a closed loop. Closed loop obstruction has been for so long considered a special variety of intestinal obstruction that it must be separately considered here, and a defence offered for the application of the findings in long experimental closed loops to cases of simple low intestinal occlusion.

Pure closed loop obstruction is clinically a rare condition in the small intestine. In strangulated hernia and in volvulus, a closed loop is isolated, but in these the vascular occlusion predominates over the double obstruction. In multiple obstructions caused by adhesions, bands, and inflammatory strictures, one or more closed loops are often isolated, but these cases are complicated by a simple obstruction above the highest occluding agent.

* Much of the argument in Chapters 5, 6 & 7 is based on closed loop experiments, and the phenomena considered there need no repetition.

Wilkie first pointed out⁽¹²⁾ that the pathological course of a closed intestinal loop depends on the degree to which its contents are infected by bacteria.

(a) If the loop contains grossly infected faecal material (as an obstructed appendix usually does) the organisms multiply rapidly, gas accumulates in the lumen, the intra-loop pressure rises rapidly, fluid and leucocytes are poured into the lumen, and a pyocele forms. Soon the increase in pressure interferes with the circulation in the loop wall, cyanosis may develop to an extreme degree, complicated by the signs of acute inflammation as the organisms invade first the mucosa (devitalised by tension) and then the muscle coat. Gangrene rapidly develops in the loop and perforation occurs to be followed by local or general peritonitis, according as there has or has not been time sufficient for the formation of limiting adhesions. This course, very common in the appendix, may be observed also in loops of small intestine isolated experimentally or clinically.^(3,4,5,8) Other things being equal, a small infected closed loop is more liable to early perforation than is a long one,⁽²⁾ perhaps because a small loop accommodates itself less

easily to a rapid increase in the volume of its content, and more rapidly develops a high pressure within it.

(b) If, on the other hand, the contents of the obstructed loop are sterile, it merely distends slowly as a mucocoele, the muscle wall having weeks or months to adjust itself to the increasing amount of mucus within it. This variety of closed loop obstruction, not rare in the appendix, can be exactly reproduced in closed loops of small intestine isolated experimentally, if the lumen is reconstructed after exclusion of the closed loop, and if the closed loop is first washed out to clear it of organisms, or sterilised by preliminary drainage to the exterior. Animals with closed loops free from infection may live indefinitely in this way. (1,4,5,6,7,8,10.12) On the other hand, closed loops with a sterile content may be fatal to the animal. This seems to be especially true where mucus secretion into the loop is rapid and associated with a sharp rise in intra-loop tension. The animal dies with a tensely distended and congested closed loop, before perforation occurs. (9) Experimental results in this connection are contradictory. Taylor's (9) work strongly suggests that intra-intestinal pressure

is an important factor even where the content of a closed loop is sterile. By two months' drainage to the exterior, Taylor sterilised closed loops so efficiently that they could be dropped back open into the peritoneal cavity without ill effect. If these sterile loops were now closed, they distended rapidly with mucus, and death followed in two to four days. The question of the sterile closed loop is still therefore sub judice, but it is true to say that the mucocoele of a sterile closed loop is not fatal unless perhaps the mucus is secreted so rapidly that the bowel wall cannot accommodate itself to the rising tension within it, and circulatory changes occur.

(c) More common in the small intestine, however, than either the sterile mucocoele, or the heavily-infected, rapidly-perforating pyocoele, is Wilkie's third type of closed loop. This variety is probably never seen in the appendix, but is the commonest type of all when a long closed loop of small intestine is isolated. This is an intermediate grade of closed loop, when organisms are present, but not in sufficient abundance to give rapid distention and perforation. The loop distends, in the course of a few days, with foul gas, and with dark brown blood-stained fluid

composed of mucus, leucocytes, fragments of dead epithelium, whole blood, and bacteria. The walls of the loop are tense and congested and oedematous, with bacterial invasion and leucocytic infiltration. The mucosa is necrotic and ulcerated as a result of the high intra-loop tension and consequent cyanosis or anaemia, the muscle coat is flabby and inflamed, and the serosa is usually congested. In such a case the animal dies before perforation occurs, and before there is more than a mildly hyperaemic degree of local peritonitis. Death is due to closed loop obstruction per se. Such a loop resembles very closely the lowest distended loop in a case of simple occlusion, and it is difficult not to believe that the cause of death is the same in both these conditions. The only difference is that dehydration, hypochloraemia, and alkalaemia, slight in low occlusion, are almost entirely absent in closed loop obstruction. *Why?*

In Experiments 10 to 16, an attempt was made to estimate the rôle played in closed loop obstruction by blood loss from the general circulation into the dilated vessels and tissue spaces of the engorged bowel wall. The duration of life in this series of seven cats, after isolation of a closed loop, and

reconstitution of the lumen around it, varied from two to six days. All the animals died with distended loops, but without perforation or peritonitis. The longer the isolated loop, the shorter was the survival period. The blood loss into the congested loop was estimated by comparing the weight of the loop, cleaned and with its mucosa dried, with the weight of an unobstructed loop of identical length. No estimation of blood loss into the lumen was possible, but in a few cases this must have been very slight, since the contents in some were light brown in colour and not blood-tinged. The blood loss estimated in this way varied from 1.3 per cent. of the blood volume, in the case of a loop one-tenth as long as the small intestine, to 11 per cent. of the blood volume where one-half of the small intestine was isolated. Such a blood loss, though appreciably greater than the loss in simple occlusion (0.6 to 5 per cent. for the whole small intestine - see page 35) and perhaps an important practical feature in closed loop obstruction, is equivalent to only a moderate external haemorrhage, and is not sufficient to explain the death of these animals. The nervous stimulation induced by distention of intestinal loops has been previously discussed (p. 36)

- it was seen that the possibility of death being due purely to sensory stimuli is a small one.

It cannot be too strongly emphasised that in closed loop obstruction, as in simple occlusion, death never occurs unless intestinal distention is present to a greater or lesser degree. If the intestinal pressure is prevented from rising, by aspiration⁽⁸⁾ or by external drainage⁽¹¹⁾ death does not occur. Even in grossly infected loops, where death is early from perforation, gangrene would not occur if the bacterial gas production did not give rise to rapid distention and to circulatory interference in the bowel wall.

Evidence has been offered above (Chapter XII) that a depressor substance is present in the portal blood after release of distention of a long closed loop. It has been suggested that this depressor substance may be absorbed by the distended bowel in simple occlusion, during those moments when upward regurgitation of content, or sudden contraction of the wall followed by relaxation, permit momentary re-establishment of the circulation. It is less easy to see what circumstances would permit a similar absorption in a closed loop, where no great alteration in intra-loop pressure is possible. In a closed loop, however,

the circulation is not equally impaired at all points on the circumference of the bowel. There may be advanced cyanosis on the antimesenteric border, while the colour remains still good, and the circulation little disturbed on the mesenteric border. Between these two extremes there must be a borderland where engorged vessels march with neighbours in which a moving stream of blood still circulates. In this boundary area it is perhaps reasonable to assume some collection by the circulating blood of diffusible substances (including our depressor) from the area of cyanosis.

In summary, a heavily infected closed loop, (especially if of short length like the appendix) perforates early and gives death from peritonitis.

A sterile closed loop forms a mucocoele, which is compatible with long survival, though in some cases, especially if rapid mucus secretion gives a high intra-intestinal pressure, even such a mucocoele may perhaps be fatal.

In the intermediate variety of closed loop, with a mildly infected content (such as most loops of small intestine have) death is due probably to the same cause as in low simple intestinal occlusion (perhaps

to absorption of a diffusible depressor substance from the edge of the still viable portion of the loop). Blood loss from the general circulation into the congested vessels of the closed loop is more important here than in simple occlusion, but is not sufficient to occasion death. In all three forms of closed loop obstruction, as in low intestinal occlusion, the importance of distention and a high intra-intestinal pressure cannot be over emphasised. In a long closed loop where bacterial content is the average bacterial content of healthy small intestine (Wilkie's third or mildly infected type) death occurs before perforation, from the same cause in all probability as death in low intestinal occlusion. In neither of these conditions does death occur unless intestinal distention is present.

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XIV. COLONIC OBSTRUCTION.

Simple occlusion of the colon in the enormous majority of cases is due to carcinoma, and since it becomes acute only after the tumour has been present for several months, the changes of acute obstruction are superimposed on those of the chronic form (with which we are not immediately concerned). Before the obstruction becomes complete, the bowel is already dilated, its muscle wall hypertrophied, and its mucosa not infrequently the seat of stercoral ulceration. In complete colonic obstruction, the pathological changes in the bowel wall are not in other respects dissimilar to those occurring in the small intestine in occlusion of that viscus. The ileo-caecal valve, however, remains competent until a late stage, and regurgitation into the small intestine occurs only when a high level of intra-colonic pressure is reached. So high indeed may the pressure rise within the colon above a stricture, that perforation of the wall - usually of the thin-walled caecum through a stercoral ulcer - is a not infrequent termination of acute obstruction of the large bowel.

When the intra-colonic pressure reaches such a degree that the ileum can no longer force its content

through the ileo-caecal junction (if indeed the patient survive so long), the small intestine distends, and the symptoms of small intestine obstruction supervene, but vomiting is a late feature, and the changes in the blood chemistry are slight.

In the experimental animal, colonic occlusion is the most slowly fatal of all forms of acute intestinal obstruction, and an animal with a complete occlusion of the rectum may survive untreated for as long as thirty days, death being apparently due to starvation. In man acute colonic obstruction is more lethal, for the patient has usually suffered for some time, with or without complaint, from a slowly progressive malignant process, his weight has decreased, his general condition is poor, and the acute obstruction occurs in a bowel already diseased. There is no significant change usually in the chlorides; the non-protein nitrogen rises gradually, and the blood urea may reach a concentration of 65 or 70 milligrams per cent. just before death. In only sixty per cent. of cases is the blood volume measurably diminished. (1)

In colonic occlusion, the same forces thus seem to be acting as are responsible for death in low small intestine obstruction, provided the patient does not

die of perforation and peritonitis before they come into play.

Obstructive appendicitis, which has been considered in Chapter XIII, is of course a closed loop obstruction of the colon, although it has been used as a parallel of experimental closed loop obstruction of the small intestine.

The third variety of acute obstruction - strangulation - is exemplified in the colon most typically by volvulus of the sigmoid. Its morbid physiology differs in no respect from that of small intestine strangulation.

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XV. STRANGULATION OF THE INTESTINE.

Strangulation, or interference with the blood supply of a bowel loop, occurs in a pure form clinically in mesenteric thrombosis and embolism, when the venous or arterial system of the bowel is occluded, without, initially, a block in the lumen. An anaemic or a cyanosed bowel, however, is incapable of transmitting its content, and the intestine above a strangulated segment soon distends as it would above a simple occlusion. In most of the clinical examples of strangulation, an occlusion of the lumen occurs at the same moment as the vascular interference - in volvulus, in intussusception and in strangulated hernia, the occlusion and the strangulation have a synchronous onset. Lastly, the distended bowel above any simple obstruction will, if it remains unperforated and if the subject survives long enough, suffer a gradually increasing interference with its circulation, passing through a stage of venous congestion and anoxaemia to death.

Theoretically, strangulation may be considered as of two separate types, an anaemic (where the arteries alone are occluded) or congestive (where only the veins

*Does this
mean -
So. Sufferer +
Gross information
books -*

suffer). Practically, however, the anaemic variety is excessively rare. The collateral circulation liberally furnished by the various arcade systems, renders almost any arterial infarct immediately haemorrhagic and if the circulatory disturbance is due to distention of the bowel, the rising intra-intestinal pressure causes first a closure of the veins and deep congestion before the anaemia of arterial compression has time to arise. "White strangulation" is seen clinically only in the middle of the small intestine extremely early in the course of cases of sudden embolism of the main trunk of the superior mesenteric artery. Experimentally an anaemic infarct can be produced by an inflation of a bowel segment to 120 or more mm. of mercury, so rapidly induced that the stage of venous stasis is passed before blood has escaped from the vessels to the tissue spaces of the wall, and the higher pressures have a chance of emptying the vessels of the wall after the arterial supply is cut off.

Superior mesenteric

The pathology of strangulation is relatively simple. The capillaries distend grossly with anoxaemic blood, as a result either of true venous congestion or of flooding by blood from collateral vessels, in

cases where the artery of direct supply has been occluded. The vessels are dark, distended, and the seat of increasing thrombosis. Peristalsis, violent during the initial congestion, ceases after a time and the muscle lies flaccid. The vascular endothelium bursts under the pressure of venous blood, and haemorrhage occurs into the perivascular spaces of the wall, the tissue plains, and the submucosa. Ultimately serosa and mucosa break in a multitude of microscopic points and blood oozes into the lumen and into the peritoneal cavity. The bowel wall swells in oedema to three or four times its thickness. Organisms from the lumen invade first the necrotic and ulcerated mucosa, then the interfascicular spaces of the muscle wall where they induce an outpouring of leucocytes, and finally reach the subserosa and peritoneal coat, whose sheen is soon hidden by a reactive layer of fibrin. The lymphatics are outlined, distended with disintegrating red blood cells and leucocytes, which, at first discharged proximally towards the thoracic duct, soon stagnate and thrombose. (13) The mesentery of the affected bowel is oedematous too, and its veins engorged. There may be petechial haemorrhages along the lines of the vessels. The local lymph glands are swollen and

over-ripe with lymph and red cells and leucocytes.

The clinical course of the case of strangulation of intestine differs little from that in acute occlusion. The initial pain is more severe in strangulation by reason of the violent movements of the cyanosed bowel. A little blood may be passed per rectum. The fall in blood pressure and in temperature, the rise in pulse rate, the collapse and the pallor are more profound in strangulation, and death is earlier. (10,14,15,19)

An animal with the veins to a loop of bowel ligated will die in less than three days - usually in less than twenty-four hours. (3,5,6,13,16,17,18)

The intensity of the collapse, and the rapidity of the fatal issue, varies directly as the length of the strangulated loop. (7,8,9,11)

The most fatal form of strangulation is when the veins alone are occluded, the artery of supply not being interfered with. (11,17,19) Death is a little delayed if both vessels are obstructed. (17)

If the artery alone is tied, death is late and, in this variety alone, due to perforation of the anaemic loop. (17)

Cause of Death in Strangulation.

The theories suggested to explain the cause of death in simple occlusion have been applied also to strangulation.

(1) Nervous Theory. Sensory nervous impulses from the strangulated bowel, however, are of little importance in strangulation. If a loop of bowel is strangulated in an animal after section of the upper thoracic spinal cord, after double intrathoracic vagotomy, or after direct division of the nerves of supply to the loop, vomiting is lessened and the animals are apparently more comfortable, but death is not delayed.

(2) Theory of Blood Loss. The amount of blood loss from the general circulation into the congested vessels of the strangulated loop, into the spaces of the bowel wall, and through the bowel wall into the lumen and general peritoneal cavity, has been widely investigated. Foster and Hausler⁽⁹⁾ found that if a loop of dog bowel, twelve inches or more in length, has its mesentery tied and is placed in a balloon to isolate it from the peritoneal cavity, life is not prolonged, although from such a loop absorption is

possible neither via the veins or lymphatics of the mesentery nor by way of the peritoneum. The blood-stained fluid poured into the balloon from such a loop has no lethal effect when injected into other animals. Scott and Wangenstein⁽¹⁷⁾ measured the blood loss by estimating the haemoglobin content of the fluid in the lumen of a strangulated loop, and of the fluid in the peritoneal cavity. To the amount of blood lost in this way (as indicated by the haemoglobin content of these) was added the increase in weight of the bowel loop after strangulation. The blood loss from the circulation by strangulation of a bowel loop was found to amount to from 34 to 66 per cent. of the blood volume - a loss comparable with a severe external haemorrhage. Holt⁽¹¹⁾ repeated Foster's work, and estimated that 50 per cent. of the blood volume could be lost in four hours after strangulation of a long bowel loop.

In Experiments 23 to 34 an attempt was made to determine the amount of blood lost in venous strangulation of the bowel in cats, by using Foster's and Hausler's rubber bag technique, and comparing the weight of the rubber bag, and strangulated bowel and blood-stained fluid within it, with a similar rubber

bag containing a normal loop of bowel of a length equal to that strangulated. Five cats had one half or more of the whole length of their small intestine (two and a half feet or more) placed in a rubber balloon, and strangulated by a ligature tied around the neck of the balloon nearly but not quite tight enough to give cessation of pulsation in the artery of supply to the loop. The lumen of the gut was reconstituted by lateral anastomosis outside the balloon and balloon and gut returned to the peritoneal cavity. Two of these animals died of peritonitis, the ligature around the neck of the strangulated loop cutting through balloon and bowel. The remaining three animals died in 6, 24, and 24 hours respectively, with balloons airtight and without peritonitis. In each case the balloon contained plum-coloured bowel distended by dark blood-stained fluid, and surrounded, within the balloon, by fluid hardly distinguishable from dark fluid blood. In these three cats, the blood loss, estimated by a comparison of the weight of the intact balloon with the weight of a similar balloon containing an equal length of normal bowel, amounted to 43 per cent., 45 per cent. and 52 per cent. of the total blood volume, - a loss sufficient in itself to

explain their early death.

Seven cats had one quarter or less of the whole small intestine (12 to 15 inches) similarly strangulated in balloons, the lumen of the bowel being again reconstituted. These, killed after 18 to 24 hours, presented a gain in weight of the balloon contents representing a blood loss of 22 to 35 per cent. of the blood volume. The longer the loop, the greater the loss of blood into it and through it. This is equivalent to a serious but not fatal external haemorrhage. In the cat, therefore, venous strangulation of one half or more of the small intestine gives early death from blood loss.

No. of Expt.	Fraction of jejunum strangulated	Wt. of Balloon + strangulated contents	Wt. of Balloon + normal loop of similar length	Wt. of Blood lost	Estimated Blood Volume	Blood loss as percentage of blood volume	Duration of life
23	Whole	185 gm.	91 gm.	94 gm.	210 cc.	45%	Died in 6 hours
24	One Half	170	60	110	210	52%	Died in 24 hours
25	One Half	220	140	80	188	43%	Died in 24 hours
26	One Half	Died of peritonitis. Ligature cut through neck of balloon					
27	One Half	Died of peritonitis. Ligature cut through neck of balloon					
28	Two-Sevenths	132	90	42	120	35%	Killed after 18 hours
29	One Quarter	193	154	39	172	23%	Killed after 24 hours
30	Two-Ninths	184	142	42	158	27%	Killed in 18 hours
31	Two-Ninths	160	107	53	165	32%	Killed in 18 hours
32	One-Fifth	142	111	31	135	23%	Killed in 18 hours
33	One-Fifth	203	151	52	188	28%	Killed in 24 hours
34	One-Seventh	173	140	33	150	22%	Died in 20 hours*

*In this animal, some escape of balloon fluid into the general peritoneal cavity accounted for its early death.

Chemical Changes in the Blood in Strangulation.

The chemical changes in the blood in strangulation are slight. Death occurs before anhydraemia, hypochloraemia and azotaemia are established in any degree.

The Toxic Effects of Strangulation.

In long loop venous strangulation death is due to blood loss from the general circulation. If a loop of medium length (one quarter or less of the whole jejuno-ileum) be strangulated, however, and excluded from the general peritoneal cavity by enclosure within a balloon, death is indefinitely postponed; the blood loss, though sometimes considerable (Experiments 28 to 34) is not sufficient to cause death. This strongly suggests the peritoneal absorption of poisonous material from medium-sized strangulated loops - a suggestion that receives support from the greater severity of internal than of external strangulation (cf. volvulus and hernia) and from the rapid collapse which sometimes follows reduction of a strangulated hernia.⁽²⁾

The fluid secreted outwards from a strangulated loop into a Foster and Hansler balloon, when injected ^u into healthy animals, gives rise to no untoward symptoms

122.

if the strangulation has been present for less than
eighteen to twenty-four hours. (11)

Relation of bacteria to the toxicity of the peritoneal transudate in strangulation.

No. of Expt.	Length of bowel strangulated	Length of survived period	Results of intra-peritoneal injection of balloon fluid	Cultures of sero muscular coat	Cultures of balloon fluid
111	Whole small intestine	Died in 6 hours	Whole amount non-toxic to guinea pig	Sterile	Sterile
112	One foot ileum	Killed in 8 hours	" "	"	"
113	One foot jejunum	Killed in 10 hours	" "	"	"
114	One foot ileum	Killed in 12 hours	" "	"	"
115	One foot jejunum	Killed in 15 hours	" "	"	"
116	One foot ileum	Killed in 18 hours	" "	"	"
117	One foot jejunum	Killed in 18 hours	" "	"	"
118	One foot ileum	Killed in 18 hours	" "	"	"
119	2½ feet jejuno-ileum	Died in 24 hours	" "	"	"
120	One foot jejunum	Killed in 30 hours	Whole amount killed cat in 8 hours (1,2,3,5)	Aerobes and Anaerobes	Aerobes and Anaerobes
121	One foot ileum	Killed in 18 hours	5 cc. killed g.p. in 8 hours (1,2,3,4) 2 cc. killed mouse in 2 hours	"	Sterile
122	2½ feet jejuno-ileum	Died in 24 hours	2 cc. killed g.p. in 4 hours (1)	"	Aerobes and Anaerobes
124	One foot ileum	Killed in 24 hours	5 cc. killed g.p. in 7 hours (1,2,3)	"	"
125	9 inches ileum	Died in 20 hours	5 cc. killed g.p. in 6 hours (1,2,5) 2 cc. killed mouse in 2 hours	"	"
126	One foot ileum	Killed in 24 hours	5 cc. killed g.p. in 8 hours (1,2,3,4)	"	"
127	One foot ileum	Killed in 20 hours	5 cc. killed g.p. in 6 hours (1,2)	"	Sterile
128	One foot ileum	Killed in 27 hours	4 cc. killed g.p. in 5 hours (1,3,4,6)	"	Aerobes and Anaerobes

Symptoms in injected animals:

- (1) Apathy, weakness, increased respiratory rate before death. P.M. no peritonitis.
- (2) P.M. marked congestion of liver and spleen.
- (3) Spastic seizure of hind limbs before death.
- (4) Intense respiratory embarrassment before death. P.M. emphysema.
- (5) Velvety red congestion of duodenum and upper jejunum.
- (6) P.M. Subendocardial haemorrhages.

Relation of Bacteria to the Toxicity of the Peritoneal
Transudate in Strangulation.

An attempt was made to relate the toxicity of the peritoneal transudate to the presence of bacteria in the strangulated bowel wall, and in the peritoneal transudate itself. (Experiments 111 to 128) In nine cats, one foot or more of small intestine in a condition of venous strangulation was isolated in a rubber balloon within the peritoneal cavity, and the animals killed after periods varying from six to twenty-four hours. In these animals the transudate into the balloon, and the sero-muscular coat of the strangulated bowel, gave no growth of bacteria in aerobic or anaerobic agar culture. Intraperitoneal injection of the transudate in guinea pigs was not followed by any signs of intoxication.

One foot of jejuno-ileum of a cat, strangulated in a balloon within the peritoneal cavity for thirty hours, remained imperforated, and furnished 30 cc. of blood-stained transudate. This transudate, and the sero-muscular coat of the strangulated bowel, gave liberal colonies of both aerobic and anaerobic organisms on agar culture. The whole collected amount of transudate, injected intraperitoneally into an adult

cat of similar size gave drowsiness and death in eight hours. No peritonitis was present in the injected animal, and autopsy failed to provide evidence of the cause of death.

Seven cats had one foot of jejunum-ileum strangulated in a balloon within the peritoneal cavity for eighteen to twenty-four hours. The seromuscular coat of the strangulated loop in each of these animals yielded a liberal growth both of aerobic and of anaerobic organisms. In five of the cats, the balloon fluid also yielded both aerobes and anaerobes on culture, but in the remaining two animals, the balloon transudate was sterile. The balloon fluid from each of the seven animals was tested for toxicity by intraperitoneal injection in guinea pigs. A dose of 5 cc. was in every case fatal in from two to eight hours, and in some cases the minimum lethal dose for a guinea pig was as little as 2 cc. Death was frequently preceded by spastic seizures of the limbs, and occasionally by intense respiratory embarrassment. In the injected guinea pigs, the post mortem appearances were neither uniform nor conclusive. None presented the appearance of peritonitis. In those whose death was delayed for more than five hours after injection, marked congestion of liver and spleen were observed;

in two guinea pigs there was a velvety red congestion of the mucosa of the abdomen and upper jejunum; in one dying in respiratory embarrassment, emphysema was noted, and subendocardial haemorrhages were present in one animal. Two of the specimens of balloon fluid were further found fatal to mice on intraperitoneal injection of doses of 2 cc. *Assadum*

Those experiments demonstrate that the toxicity which develops after eighteen to twenty-four hours in the peritoneal transudate of strangulated cat intestine is associated with the passage of bacteria into the seromuscular coat of the necrotic bowel wall. The presence of bacteria in the toxic transudate is usual but not invariable, and apparently not essential for the development of toxicity. These experiments parallel the experiments of Holt⁽¹¹⁾ who found that the pressure of fluid within the strangulated loop remained steady for about twenty hours, when it began to fall, while the non-protein nitrogen, rising steadily in the bowel content from the start, began to rise in the balloon fluid only twenty hours later. That is, the bowel wall becomes permeable to bowel content only twenty hours or so after strangulation. Holt found such small quantities of fluid lost, *=*

however, from the bowel lumen, that he considered these not responsible for death, and inclined to the view that the toxicity of the peritoneal fluid in the later stages of strangulation is due to the outward passage of toxins elaborated by bacterial invaders of the necrotic bowel wall. Experiments 111 to 128 strongly suggest that in medium-sized strangulated loops in which the fall in blood pressure from blood loss is not fatal, bacteria invade the seromuscular coat of the bowel after eighteen to twenty-four hours, and pour outwards into the general peritoneal cavity a toxin whose absorption is responsible for death in these cases.

Numerous experiments have been performed by others to demonstrate that strangulation of the intestine is not fatal provided the strangulated loop is sterile, and provided the gastro-intestinal canal is reconstituted with exclusion of the strangulated loop. von Albeck,⁽¹⁾ taking advantage of the absence of organisms from the gastro-intestinal tract of hibernating hedgehogs, strangulated 20 cm. of the intestine of one of those animals. The hedgehog awakened two days later, and remained apparently comfortable, eating and drinking. Death occurred only on the sixth day. Kirstein⁽¹²⁾

performed the same experiment. Again death occurred only on the sixth day, and after death, organisms were found throughout the whole gastro-intestinal tract. Dragstedt, Moorhead and Burcky⁽⁵⁾ isolated closed loops of dog jejunum and sterilised the lumen with ether. Complete occlusion of the vessels was then followed by no ill effects.

The freedom from organisms of the gastro-intestinal tract for a short time after birth offers a simple method of demonstrating the importance of bacteria in strangulation.

Five guinea pigs (Experiments 129 to 133) were subjected to aseptic laparotomy at the ages of 8 hours, 32 hours, 56 hours, 72 hours and 96 hours respectively. In these animals the small intestine was ligated at each of its ends as a closed loop, and the superior mesenteric vein was clamped. As soon as the long closed bowel loop became dusky in colour it was excised with ligation of its mesentery, and laid with aseptic precautions in the peritoneal cavity of a cat. Cultures were made of the contents of the guinea pig bowel before this transposition. The condition in the cat now closely resembled strangulation of a bowel loop, with its blood supply completely cut off, but

with peritoneal absorption still possible. The difference in species of strangulated gut and host did not lessen the risk of death from toxæmia.

The contents of the intestine of the three youngest guinea pigs, aged 8 hours, 32 hours and 56 hours, were sterile on aerobic and anaerobic culture. The three corresponding cat hosts lived indefinitely, and when they were killed and autopsied, one to three months later, offered no trace of the transplanted guinea pig bowel, with the exception, in one animal, of a few adhesions binding the omentum to the parietal peritoneum of the anterior abdominal wall.

The bowel content of the other two guinea pigs, aged 72 and 96 hours, yielded both aerobic and anaerobic colonies on agar culture. The cat hosts of these strangulated loops died in twenty-four and twenty hours respectively. In neither of these animals was the necrotic bowel loop perforated, and in one of them only was there a mild local peritonitis.

This short series of experiments offers strong proof that bacteria are essential for the development of the toxæmia of intestinal strangulation.

h

The Chemical Nature of the Toxic Elements of the
Transudate from Strangulated Intestine.

(a) The Protein Fractions. A protein separation was performed on several specimens of balloon fluid of proved toxicity from intestinal loops strangulated for twenty to twenty-four hours. The euglobulin, globulin and albumin fractions (the last containing any proteose present) were precipitated respectively by one-third saturation, half saturation, and complete saturation with ammonium sulphate and collected by filtration. The resultant filtrate contained any peptone present. The three precipitated fractions were redissolved in physiological saline solution without drying, and all four fractions were freed of ammonium sulphate and of diffusible non-protein content by dialysis through celloidin for four days with three daily changes of dialysate.

These various fractions were tested for toxicity in mice and guinea pigs (Experiment 124). In no case was the injection of the globulin, albumin and peptone fractions attended by the symptoms of poisoning, though in each instance, the amount injected represented the globulin or albumin or peptone fraction of the whole balloon fluid from a single strangulated cat.

On the other hand, ten guinea pigs injected intraperitoneally with the extracted euglobulin corresponding to $1/10$ to $1/2$ of the balloon transudate from a single strangulated cat died in from four to eight hours: in these animals death was preceded usually by spastic seizures of the limbs, and post mortem the liver and spleen were congested: in one animal there was in addition a patchy congestion of the mucosa of the small intestine. In a minority of cases there was haemolytic staining of the endocardium and aortic intima. Three guinea pigs similarly injected with doses of euglobulin solution corresponding to $1/10$ to $1/5$ of the total balloon fluid from a single strangulated loop remained for a few hours in a state of glassy-eyed torpor interrupted by spastic seizures of the limbs, but recovered. Four guinea pigs injected with the euglobulin of one tenth to one fiftieth of the balloon fluid from a single loop showed no signs of poisoning. The euglobulin solution was similarly found to be toxic to mice. Numerous control injections in mice and guinea pigs of comparable doses of the euglobulin fraction of normal cat blood, and of the euglobulin fraction of non-toxic transudate from early strangulated intestinal loops were followed neither by

death nor by any symptoms of intoxication. The toxic properties of the euglobulin solutions prepared above were not present after coagulation of the euglobulin in the solution by boiling.

(b) The Non-Protein Fraction. A protein-free extract of toxic twenty-four hour balloon transudate from several cats was obtained by adding trichloroacetic acid to a concentration of 10 per cent., leaving one to two hours, filtering, and extracting the filtrate four or five times with ether: 10 cc. of this extract corresponded to the transudate recovered from one strangulated cat loop. Eight young guinea pigs (150 - 250 gm. in weight) (Experiment 136) injected intraperitoneally with 2 to 10 cc. of the non-protein filtrate died in from two minutes to one hour, with respiratory embarrassment in every case. Smaller doses were not lethal. Intraperitoneal injection in guinea pigs of a similarly prepared protein-free filtrate of cat blood, and of non-toxic balloon fluid from early strangulated loops was followed by no ill effects. It can therefore be concluded that in the peritoneal

transudate from a strangulated intestinal loop there are two toxic elements. One of these is non-diffusible and is precipitated with the euglobulins. The second is diffusible and present in a protein-free filtrate of the transudate.

The Biological Activity of the Toxic Elements of the Peritoneal Transudate from Strangulated Intestinal Loops.

(a) The Euglobulin Fraction. (Experiment 137)

Intravenous injection of the toxic euglobulin fraction prepared above had a variable effect on the blood pressure of the dog, being followed most often by no alteration in blood pressure, occasionally by a fall in pressure, on one occasion by a rise in pressure, and in a few cases by wild upward and downward variations. These effects obtained whether ether or chloralose was used for anaesthesia. Intravenous injection of the toxic euglobulin fraction had no effect on the blood pressure of the rabbit.

(b) The Protein-Free Filtrate. (Experiment 138)

5 cc. injected intravenously in a dog under ether anaesthesia gave a fall of blood pressure from 146 to 30 mm. of mercury in forty seconds and death in two

and a half minutes (Fig. 18). This dose corresponded

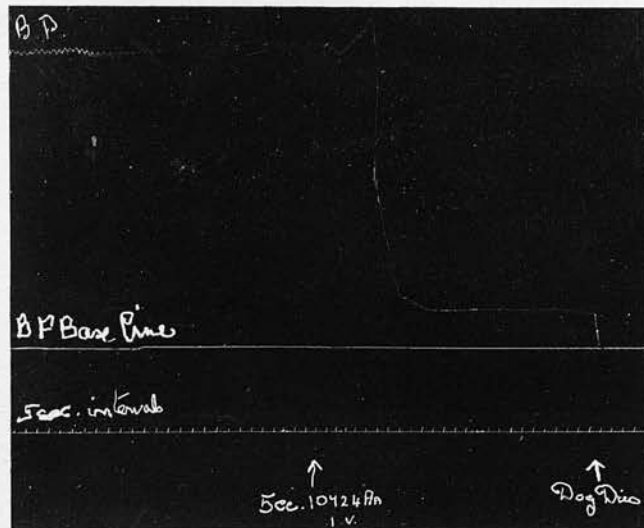


Fig. 18. Effect on B. P. of dog of 5 cc. protein-free filtrate of peritoneal transudate from a loop of dog intestine during 24 hours venous strangulation.

to one half of the filtrate from a single cat loop, strangulated for twenty-four hours. In two other dogs intravenous injection of 1 cc. of the extract gave less pronounced, but still well marked depressions of the blood pressure curve (60 and 71 mm. of mercury respectively): the blood pressure of the last two animals recovered again from this depressor effect (Figs. 19 and 20).

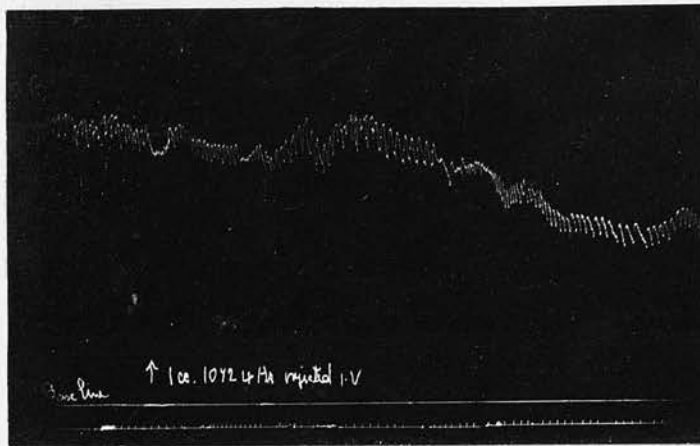


Fig. 19. Effect of B. P. of dog of 1 cc. of protein-free filtrate from peritoneal transudate of a strangulated loop.

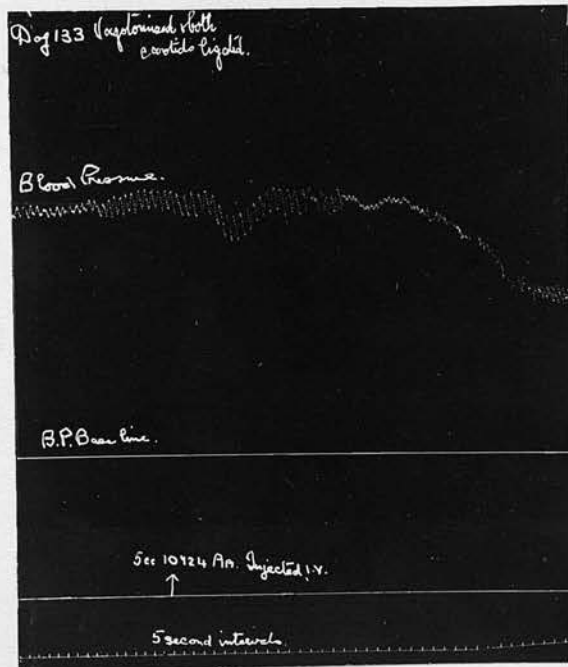


Fig. 20. Effect of B. P. of dog of 5 cc. of same filtrate.

The filtrate, in even larger doses, had no effect on the blood pressure of the etherised rabbit. The filtrate had no effect upon the eserinated rectus abdominis of the frog, nor upon eserinated leech muscle (which contract under the influence of acetylcholine), but induced a marked contraction (a very characteristic histamine effect) of the isolated uterus of the virgin guinea pig in a concentration of one part of the filtrate to five hundred parts of saline (Fig. 21).

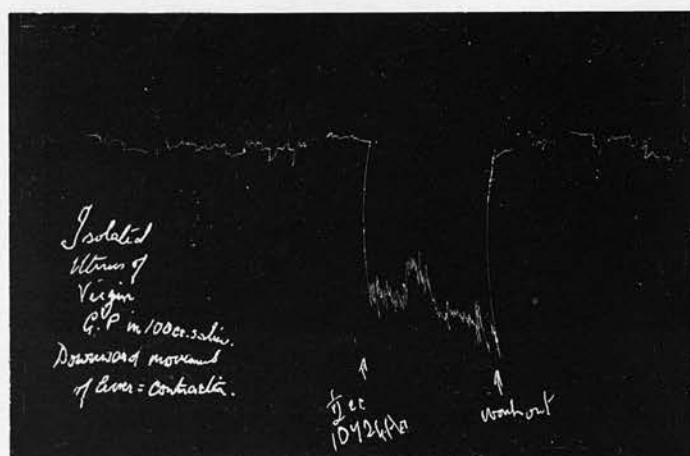


Fig. 21. Effect on virgin guinea pig uterus of protein-free filtrate of "strangulation transudate" in concentration of 1 part of filtrate to 200 parts saline.

In a similar concentration, the filtrate increased the

motility of isolated cat jejunum (as histamine does) but had no effect upon the small intestine of the rabbit, which is stimulated by adenosine. The Pauly reaction for the presence of histamine was negative. A similar protein-free filtrate of non-toxic transudate from an early strangulated loop, had no effect on the blood pressure of the dog, on the guinea pig uterus, or on isolated cat jejunum.

These biological effects were so suggestive of the presence of histamine in the transudate (in spite of the negative Pauly reaction) that a crude histamine extract of the transudate was prepared: 13 cc. of fresh balloon fluid of established toxicity had alcohol added to 80 per cent. and was allowed to stand on ice for twenty-four hours. Three volumes of acetone were then added, and the precipitate obtained on filtration dissolved in 20 cc. of saline. This extract also failed to give a Pauly reaction (which, as Dale⁽²⁾ points out, is frequently absent in animal tissues known to contain histamine). 3 cc. of this extract intravenously gave a fall of blood pressure in the dog (Figs. 22, 23).

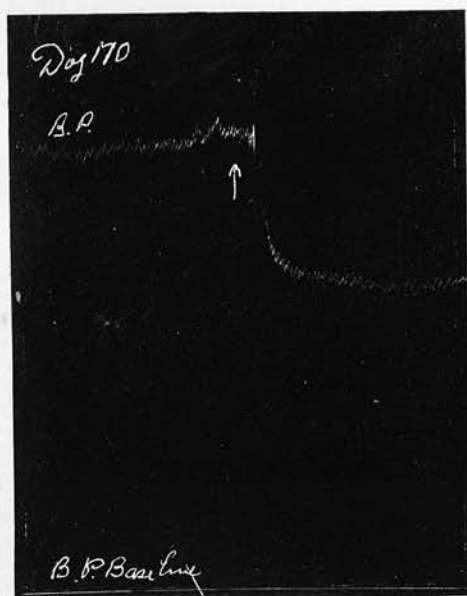


Fig. 22. Effect on B. P. of dog of 8 cc. histamine extract of peritoneal transudate from a 24-hour strangulated loop.

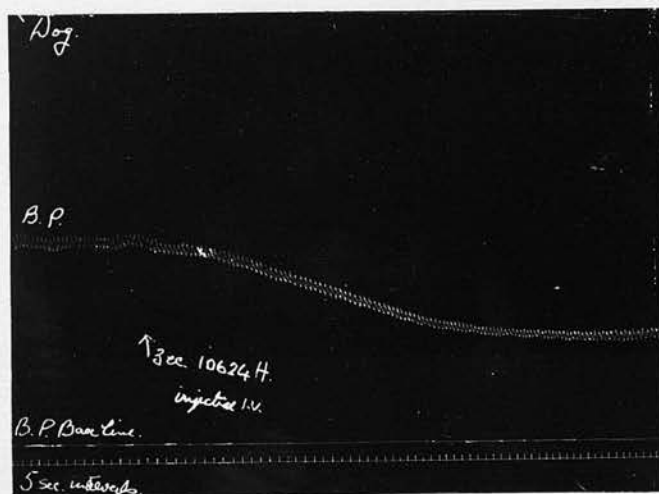


Fig. 23. Effect on B. P. of dog of 3 cc. histamine extract of transudate.

The extract in a concentration of 1 in 500 gave marked contraction of the isolated guinea pig uterus (Fig. 26) and greatly increased contraction of the

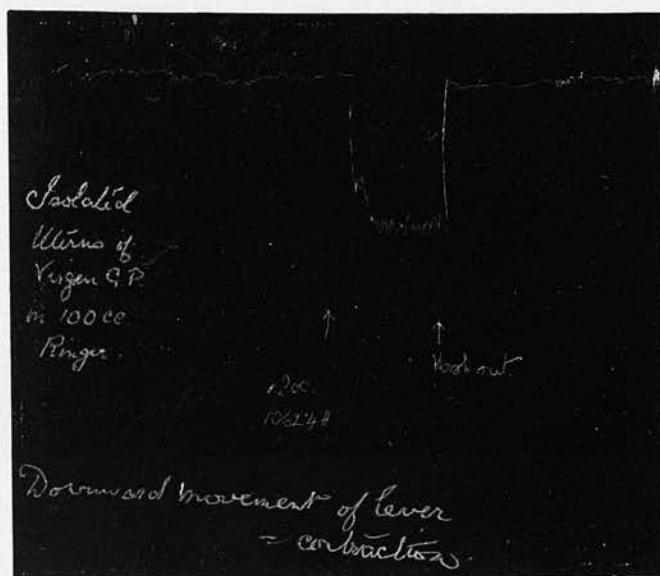


Fig. 26. Effect on virgin guinea pig uterus of histamine extract of peritoneal transudate in concentration of 1 in 500.

isolated cat jejunum (Figs. 24, 25). It had no effect upon the blood pressure of the etherised rabbit, or upon isolated rabbit intestine.

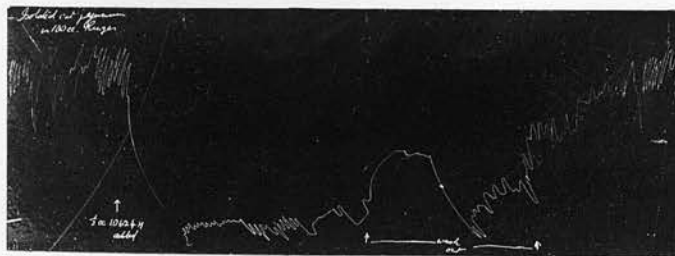


Fig. 24. Effect on isolated cat jejunum of histamine extract of peritoneal transudate in concentration of 1 in 200. Downward movement signifies contraction.



Fig. 25. As Fig. 24.

CONCLUSIONS.

It is thus confirmed that death in strangulation of a long loop of intestine is early and due to loss of blood from the circulation into the wall of the strangulated bowel, into the lumen, and into the peritoneal cavity. In strangulation of loops of medium length death is due not to blood loss but to absorption by the peritoneum of a toxic transudate from the strangulated bowel. The fluid poured into the peritoneal cavity from the strangulated loop becomes toxic only after strangulation has been present for eighteen to twenty-four hours, when bacteria have invaded the wall of the bowel and, usually but not invariably, when they have passed beyond the bowel wall into the peritoneal cavity itself. Strangulation is not a fatal condition if the bowel involved is free of organisms, provided of course, the lumen of the intestinal tract is reconstituted to prevent a complicating simple obstruction. The toxicity of the peritoneal transudate from a strangulated intestinal loop apparently depends on the presence of at least two constituents, both evolved as the result of bacterial activity. One of these is precipitated with the euglobulin fraction of the transudate, a property

which suggests a relationship with the more elaborate bacterial toxins. The other toxic constituent is diffusible, is not of a protein nature, is precipitated from alcohol by acetone, and has the biological properties of histamine.

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XVI. GENERAL CONCLUSIONS.High Intestinal Obstruction.

In high intestinal obstruction death is due to vomiting, with the dehydration, hypochloraemia, alkalæmia and azotaemia which follow in its train.

Low Intestinal Obstruction.

These changes in the blood chemistry are themselves lethal only in obstruction of the lower duodenum or upper jejunum; they occur in low intestinal obstruction (the common clinical form) only in a mild degree, and in that condition death may occur before any changes in blood chemistry are demonstrable.

In low obstruction, the blood loss from the general circulation into the cyanosed wall of distended bowel loops is trivial, and insufficient to explain the fatal outcome of an untreated case.

In low obstruction, the bulk of the evidence does not support the theory that death may be due purely to over-stimulation of the afferent nerves, though recent work suggests that such nervous influences may play at least a subsidiary part in the prostration which accompanies intestinal distention.

Death in acute intestinal occlusion is not due

to the passage of toxic content through the whole thickness of the cyanosed bowel wall, and its absorption by the peritoneum, since death is not prevented by excluding the distended bowel from the peritoneal cavity.

Artificial distention of the whole small intestine of an experimental animal is followed by cyanosis of the distended gut, stagnation of venous blood in the bowel wall and a fall in blood pressure from depletion of the available circulating blood: this depressor effect may be preceded by a transient rise in blood pressure if the distending bowel contracts on its increasing content forcefully enough to empty the vessels suddenly, increasing temporarily the venous return to the right heart, and reducing the capacity of the capillary bed.

If an intestinal distention sufficient to induce cyanosis of the bowel wall, be maintained for six to eight hours, and then be suddenly released, the cyanosis disappears, the intestinal vessels empty, the blood return to the right heart and general circulation is augmented, and the blood pressure rises. This pressor effect is not prevented by section of the afferent nerve paths from the bowel.

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If an intestinal distention sufficient to give cyanosis of the bowel wall be maintained for more than eighteen or twenty-four hours, thrombosis develops in the bowel wall, and sudden release of the distention is followed by no alteration in the blood pressure - there is no increased return of blood from the bowel to the general circulation.

If an intestinal distention sufficient to give cyanosis of the bowel wall, be maintained for more than six to eight hours, but be released before thrombosis is general in the intestinal vessels, although the cyanosed bowel pales and its imprisoned blood returns to augment the volume of circulating fluid in the vascular system, the deflation is followed not by a rise in blood pressure, but by a fall.

This fall in blood pressure is not prevented by denervation of the bowel, and can be due only to depressor properties acquired by the blood during its delayed and anoxaemic passage through the capillary bed of the congested and suffocated bowel.

Blood collected from the portal vein of a dog immediately after release of a twelve-hour distention of the whole small intestine will, if injected

intravenously in a second dog, exercise a depressor effect on the blood pressure of the injected animal.

The depressor properties of portal blood collected in this way are lost by dialysis, are absent from the precipitate brought down by saturation with ammonium sulphate, and are still present after removal of the blood proteins by trichloroacetic acid precipitation: they are destroyed by alkaline hydrolysis, unaffected by neutral or acid hydrolysis, or by de-amination. The depressor elements of the active portal blood are not precipitated from alcoholic solution by acetone.

The protein-free filtrate of active portal blood failed to give the Pauly reaction for histamine: it exercised a depressor effect on the blood pressure of the etherised rabbit, even after previous atropinisation of the animal: the filtrate had no effect upon rabbit intestine, upon frog rectus abdominis, upon eserinated leech muscle, upon the uterus of the virgin guinea pig or upon cat jejunum.

The diffusible depressor substance apparently present in portal blood immediately after release of a twelve-hour intestinal distention has not been

specifically identified, but it bears a closer relationship, in its chemical and biological properties, to the substance P of Euler and Gaddum than to histamine, acetylcholine, or adenosine.

The presence of a depressor substance in the portal blood draining a still distended bowel has not been proved. Return of such a depressor from small intestine subjected to simple occlusion, can only occur if, during the relaxation which follows upward propulsion of the content of a distended and cyanosed loop, the venous circulation is temporarily re-established in that loop. It is impossible to predict when such a momentary re-establishment of circulation is likely to occur.

Whether the depressor substance passes to the blood in the congested capillaries of a distended and cyanosed loop from an altered metabolism of the anæmic tissues of the bowel wall, or whether it passes from the lumen to the almost stagnant blood in the engorged mucosal capillaries, is a matter only for conjecture.

Closed Loop Obstruction. Death occurs in a heavily infected closed loop of intestine by gangrene, perforation, and peritonitis.

Death does not occur in a sterile closed loop if mucus is secreted slowly enough for the wall of the loop to expand as a mucocele, and accommodate it without too great an elevation of intra-intestinal pressure. There is some recent evidence that death may result in a sterile closed loop, if the pressure within it rises more rapidly than the bowel wall can expand to accommodate it.

In a closed loop with a mildly infected content, death occurs before perforation of the wall, when the loop resembles closely one of the loops of an intestine subjected to simple low occlusion. Death in such a loop is not prevented by its exclusion from the peritoneal cavity, provided there be no interference with the blood supply. In closed loop obstruction, as in low intestinal obstruction, death is invariably preceded by the development of a high intra-intestinal pressure, and increased tension of the bowel wall.

If the same depressor substance is responsible for death in the case of a mildly infected closed loop, as operates after the relief of intestinal distention, it must pass into the capillaries on the receding boundary of a still viable portion of bowel wall - capillaries which still drain, however, slowly

and inadequately, the tissue spaces of adjacent but already cyanosed bowel.

In venous strangulation of a long loop of bowel - more than one quarter of the small intestine in the case of the cat - half of the blood volume of the animal may be poured into the lumen, the tissue spaces of the strangulated bowel wall, and the peritoneal cavity. Death is then due to loss of circulating blood, and long loop ~~obstruction~~ ^{strangulation} is virtually a variety of internal haemorrhage.

In strangulation of a shorter loop, the blood loss may be still considerable, but not sufficient to account for death. Death in such a strangulation can be prevented by enclosing the affected loop in a rubber balloon, and so excluding it from the peritoneal cavity.

In such a balloon, containing a strangulated loop, blood-stained fluid collects; this fluid transudate would, in the absence of the enclosing balloon, be poured into the general peritoneal cavity, and its constituents absorbed.

The injection of the fluid content of a balloon enclosing a strangulated loop, is lethal to other animals only if the strangulation is of eighteen to twenty-four hours duration. If injection of the

balloon transudate into healthy animals is followed by death, then the seromuscular coat of the parent strangulated loop will invariably provide on culture a growth of aerobic and of anaerobic organisms, as will usually, but not invariably, the transudate itself.

No symptoms follow strangulation of a sterile loop; a strangulated sterile loop is capably dealt with by intra-peritoneal autolysis.

In transudate from a bowel loop strangulated for twenty-four hours can be demonstrated at least two constituents whose injection into other animals is lethal. One of these is a euglobulin, or is, at least, carried down with the euglobulins in ammonium sulphate precipitation as are certain of the more elaborate bacterial toxins. The other lethal constituent is diffusible, and possesses several of the chemical and biological properties of histamine.

Since strangulation of a sterile bowel loop is unattended by serious symptoms, since the non-toxic transudate from early strangulated loops is sterile, and since the toxic transudate of later strangulated loops is associated with bacterial invasion of the bowel wall and sometimes even of the transudate, it is justifiable to conclude that both the toxic elements of the transudate must have a bacterial origin.

XVII. CERTAIN PRINCIPLES IN THE TREATMENT
OF ACUTE INTESTINAL OBSTRUCTION SUG-
GESTED BY RECENT EXPERIMENTAL
RESEARCH.

High Obstruction.

In obstruction of the duodenum or uppermost jejunum death is due primarily to anhydraemia and hypochloraemia. The essential preliminary to the operative relief of the obstruction is the replacement of lost water and chloride by intravenous administration of physiological saline solution, continued and repeated till chlorides return to the urine. If the addition of a few drops of silver nitrate to the urine, with a drop of nitric acid, brings down a white precipitate, then chlorides are again being excreted, the blood chlorides have risen to a safe level, and the reaction of the blood has in all likelihood stabilised at its normal figure; if no precipitate comes down, then more saline is required. Intravenous saline administration is established now as the standard pre-operative treatment of high intestinal obstruction, but this simple test for the degree of hypochloraemia is still not generally used, and saline is still given

in cases of high obstruction in miserly and quite inadequate amounts.

Since gastric distention, and the nausea which accompanies vomiting, both increase the secretion of all digestive juices, the stomach should be kept empty in high obstruction by suction drainage through a nasal tube, or by frequent gastric lavage. The former is less likely to increase the amount of digestive secretion than is the retching which accompanies the passage of a large stomach tube.

Low Obstruction.

In low intestinal obstruction dehydration and hypochloraemia are usually not of prime importance, but if vomiting is persistent, or if the upper jejunal loops are greatly distended, there is likely to be some loss of fluid and electrolytes, and the administration of saline is then indicated. The amount given will again depend on frequent examination of the urine for chloride. The more elaborate methods of estimating the volume of saline required (such as determination of the blood chlorides, of the carbon-dioxide combining power, or of the non-protein nitrogen of the blood) cause unnecessary delay.

Hypertonic saline should never be given before relief of an obstruction. On numerous occasions,

death has immediately and dramatically occurred during the intravenous infusion of 12% or 15% sodium chloride solution. Hypertonic saline, when introduced into the circulation, is one of the most powerful known stimulants of intestinal muscle, and will flog exhausted bowel into extravagant peristalsis when other stimulant measures fail. It is not unlikely that the death which has frequently followed hypertonic saline injection, is due to powerful contraction occurring in a cyanosed bowel, and squeezing from its congested vessels, blood laden with the depressor substance which can be demonstrated in portal blood after release of an intestinal distention of six to twenty-four hours duration (Chapters VIII & IX).

It has been seen that release of an intestinal distention of only six or eight hours duration is followed by increased venous return to the heart, and a rise in blood pressure (Chapter VIII). This suggests that the essential treatment of early low intestinal occlusion should be immediate release of the obstruction, or rapid evacuation of the distended bowel by anastomosis or drainage.

If experimental distention has been present for more than six or eight hours, its sudden relief is

followed by the return of portal blood to the general circulation, carrying in it a diffusible depressor substance collected during its stagnation in the distended vessels of the bowel wall. Sudden relief of a distention of this duration has probably been the cause of collapse and death which has so often followed operations for acute obstruction in man. To prevent too sudden return of intestinal blood endowed with depressor properties, gradual decompression of the distended bowel is indicated, in addition to release of the obstruction. This decompression can be effected to some extent by the Wangensteen nasal suction tube, but such a method of decompression empties only the upper few feet of jejunum, and fails to tap the lowest and most distended loops. Better is tube drainage to the exterior of the most distended loop, a small amount of bowel content being permitted to escape at frequent intervals over a period of several hours. The segment of gut to be drained can be isolated by clamps at operation until the drain is anchored by purse string suture, gas escape and too rapid deflation being thus prevented.

If gross distention is at operation found to be restricted to a short length of bowel, primary resection of the distended segment would prevent return

from it of actively-depressor venous blood.

Resection of distended, though viable, short loops in low obstruction has indeed been advocated recently on other grounds.

The third degree of intestinal distention, when thrombosis has already occurred and gangrene is imminent or established, though easy to produce in the experimental animal, is rare in man. It requires resection.

Closed Loop Obstruction.

(I) Heavily infected closed-loops (such as the obstructed appendix) demand removal, to prevent perforation and peritonitis. (II) Sterile closed loops, if sufficiently tense to cause symptoms and so occasion operation for pain, should be removed for relief of the pain. (III) Mildly infected closed loops, if small and in the first eight hours of distention, should have their limiting obstruction released or anastomosis performed; loops distended for a longer period should be resected to avoid return from them of actively depressor venous blood. If the loop is large, decompression is as necessary here, and for the same reasons, as in the later cases of low obstruction. If found at operation only six or eight hours after the

onset of distention, release of the limiting obstructions would be the treatment of choice. If that were impossible, anastomosis or immediate drainage would be permissible. It must be remembered that in man, these mildly infected closed loops are almost invariably complicated (e.g. in multiple tuberculous strictures) by a simple occlusion above the highest stricture, and this too would demand treatment.

Adynamic Ileus.

In the rare cases where true paralysis of the intestine occurs in the absence of mechanical obstruction, it is often found at operation that the highest loops of intestine are the most distended. Vomiting in these cases is usually considerable, fluid loss, with all its consequences, is often marked, and the condition is best treated as one of high obstruction.

Strangulation.

In all cases of strangulation there is some blood loss from the general circulation into the congested bowel, and blood transfusion is accordingly desirable as a pre-operative measure. The longer the strangulated loop, the more urgent is the need for transfusion.

From a very short and still viable strangulated loop (such as is found in the average external hernia

for instance) there is, on release of the strangulation, only a comparatively small amount of depressor venous blood returned from the recovering bowel, there is as yet no toxic transudate into the peritoneal cavity from the strangulated loop, and resection is unnecessary. If the strangulation has been present for more than eighteen to twenty-one hours, bacteria have already invaded the muscle coat of the bowel wall, and toxic material is being poured into the peritoneal cavity, even if gangrene is not obvious. Such a loop must be resected.

From longer, though still viable, strangulated loops (as perhaps in intussusception and some cases of volvulus), there may be, on release of the strangulation, a dangerous amount of actively depressor blood returned to circulation.

It may be concluded that in the case of these long loops, primary resection (supplemented by liberal blood transfusion - to replace the blood removed with the engorged bowel) would be well advised at any stage of the disease, even before the toxic elements of the loops begin to be passed into the peritoneal cavity.

In strangulated loops already the seat of gangrene, resection remains, as always, the procedure of choice, with extraperitonealisation its only alternative.

Summary of Suggestions for Treatment of the
various forms of Acute Intestinal Obstruction.

A. High Obstruction.

Liberal administration of physiological saline; operative relief of the obstruction as soon as chlorides appear in the urine; nasal suction drainage.

B. Low Obstruction.

Preoperative saline, and operation only when chlorides reappear in the urine; nasal suction drainage.

- (1) If the distention of less than eight hours duration, release of obstruction.
- (2) If the distention is of more than eight hours, then.-
 - (a) Release of obstruction + gradual decompression of obstructed bowel, or
 - (b) Release of obstruction + resection of most distended loop.
- (3) If thrombosis is present, resection of thrombosed segment.

C. Closed loop Obstruction.

- (1) Heavily infected - immediate removal of loop.
- (2) Sterile - removal to prevent high intra-loop pressure, and the symptoms which result from it.
- (3) Mildly infected.-
 - (a) Small loops - resection.
 - (b) Long loops distended less than eight hours - release of obstruction, anastomosis, or immediate drainage.
 - (c) Long loops distended more than eight hours - resection or gradual decompression.

D. Strangulation.

- (1) Loop still viable, but congestion present less than twenty-four hours.-
 - (a) Short loop - relief of strangulation: blood transfusion optional.
 - (b) Long loop - liberal transfusion followed by resection or extraperitonealisation with reconstruction of lumen.
- (2) Loop still viable, but congestion present more than twenty-four hours.- blood transfusion and resection, or extraperitonealisation with reconstruction of lumen.
- (3) Loop no longer viable.- resection.

EXPERIMENTAL DETAIL.

1 - 9. Experiments to show the amount of blood
loss from splanchnic congestion in simple
intestinal occlusion in the cat.

(See page 34 of thesis)

1. 1:10:34. Cat. Weight 1500 gm. Open ether. Median abdominal incision. Caecum and ileum withdrawn. One seromuscular knot of silk was tied in wall of bowel three inches above ileo-caecal valve. One foot above this, a tape was tied round ileum to occlude it completely. One foot above the constricting tape, a second seromuscular knot of silk was inserted in the bowel wall. One sero-muscular knot thus bounded one foot of unobstructed ileum below the constricting ligature, the second silk knot bounded an equal length of obstructed bowel above the ligature. Abdomen closed after return of both loops to peritoneal cavity. Cat starved after operation.

3:10:34. Prostration, vomiting, and death in 48 hours.

Post-mortem.- No free fluid in peritoneal cavity. Intestines removed with ligation of mesentery.

Intestine below obstruction pale, empty, and contracted. Intestine above grossly distended with brown fluid (too light to be blood-stained - negative benzi-dine reaction), darkly cyanosed but not gangrenous, and still viable immediately above obstruction - no ulceration of mucosa.

Fluid content of both measured loops washed out and lumen dried by the passage of a cotton pull-through.

Weight of unobstructed foot of ileum = 9.2 gm.

Weight of obstructed foot of ileum = 10.1 gm.

Weight of fluid and blood excess in wall of obstructed foot of ileum = 0.9 gm.

But blood volume = (approx.) 7.5 per cent. of body weight

$$= \frac{7.5}{100} \times 1500 = 112 \text{ cc.}$$

So blood loss and fluid loss into lowest obstructed foot of ileum = 0.8 per cent. of blood volume.

Length of small intestine = 4 ft. 6 inches.

Therefore even if whole obstructed bowel is as suffused as its lowest foot (which it is not) and if gain in weight is from excess of blood alone, maximum blood loss into wall of gut is less than $3\frac{1}{2}$ per cent. of blood volume.

2. 1:10:34. Cat. 2000 gm. Operation as for previous cat, but linen used for constriction instead of tape. Starved after operation.

4:10:34. Prostration and death without vomiting.

Weight of lowest obstructed foot of ileum = 13.2 gm.

Weight of unobstructed foot of ileum = 12 gm.

Gain in weight of obstructed foot = 1.2 gm.

But blood volume of animal = 7.5 per cent. of 2000
= 150 cc.

Therefore excess of blood and fluid in wall of
obstructed foot of ileum = $\frac{1.2 \times 100}{150}$

i.e. 0.8 per cent. of blood volume.

But length of small intestine = 4 feet,

so if corrected to represent maximum blood loss into whole obstructed small intestine (see Expt. 1) this is less than 3.2 per cent. of the blood volume.

3. 1:10:34. Cat treated as in previous experiment. Body weight 1500 gm.

7:10:34. Died 150 hours after establishment of obstruction. Post-operative course and post-mortem findings as in previous two animals.

Weight of lowest foot of obstructed bowel = 11.2 gm.

Weight of unobstructed foot below obstruction = 10.1 gm.

Gain in weight = 1.1 gm.

But blood volume = 7.5 per cent. of 1500 = 113 cc.

Therefore excess of fluid and blood in obstructed foot represents $\frac{1.1 \times 100}{113}$ i.e. less than one per cent of the blood volume.

But length of whole small intestine = 4 feet.

So this, if corrected to represent the maximum possible blood loss into the whole obstructed small intestine (see Expt. 1) is less than 4 per cent. of the blood volume.

4. 1:10:34. Cat. Weight 3300 gm.

Operation as in Expt. 2.

6:10:34. Died without much vomiting. Post-operative course and autopsy findings as in previous animals.

Weight of lowest obstructed foot of bowel = 12.1 gm.

Weight of unobstructed foot = 9.6 gm.

Therefore excess of blood and fluid in wall of obstructed foot = 2.5 gm.

But blood volume = (approx.) 7.5 per cent. of 3300
= 247.5 cc.

Therefore excess of blood and fluid in obstructed loop = $\frac{2.5 \times 100}{247.5} = 1$ per cent. of blood volume. But the length of whole small intestine = 5 feet. So maximum blood loss possible into wall of whole obstructed small intestine is 5 per cent. of the blood volume.

5. 2:10:34. Cat. Weight, 2300 gm. Operation as in Experiment 2. Fed after operation. Ill and uncomfortable, but not vomiting, for two days, refusing food. Subsequent return of appetite and recovery.

27:10:34. Appetite poor. Apathetic. Lies curled up. Died.

P.M. Constricting silk has remained in place, but has obstructed bowel incompletely - fluid content can be squeezed through. Bowel below collapsed. Bowel above dilated by dark faecal content, thick-walled, apparently hypertrophied for 12-15 inches, then gradually returns to normal in the upper reaches.

6. 2:10:34. Cat. Weight 2700 gm. Operation as in Expt. 2, but complete recovery followed. Apparently ligature had cut through with reconstitution of the lumen.

7. 25:3:35. Cat. Weight 2900 gm. Operation as in Expt. 2. Starved after operation.

27:3:35. Died 48 hours after establishment of obstruction. Whole small intestine greatly distended, but especially the lowest foot.

Weight of undistended foot of ileum = 11.3 gm.

Weight of lowest distended foot = 11.53 gm.

Therefore excess of blood and fluid in wall of lowest obstructed foot = 0.23 gm.

But blood volume = 7.5 per cent. of 2900 = 218 cc.

Therefore excess of blood and fluid in wall of lowest obstructed foot = $\frac{0.23 \times 100}{218}$ i.e. less than 0.11 per cent. of blood volume.

But length of whole small intestine = $5\frac{1}{2}$ feet.

So this loss if corrected to apply to the whole small intestine (see Expt. 1) represents a maximum possible blood loss of less than 0.6 per cent. of the blood volume.

8. 25:3:35. Cat. Weight 2400 gm. Operation as in Expt. 2.

28:3:35. Died after 72 hours.

Weight of unobstructed foot of ileum = 7.6 gm.

Weight of lowest obstructed foot = 9.3 gm.

Therefore excess of blood and fluid in lowest
obstructed loop = 1.7 gm.

But blood volume = 7.5 per cent. of 2400
= 180 cc.

Therefore excess of blood and fluid in lowest obstructed
loop = $\frac{1.7 \times 100}{180}$ i.e. less than 1 per cent. of the
blood volume.

If this is corrected to represent the maximum possible
blood loss into the whole obstructed small intestine
(length $5\frac{1}{2}$ feet) this is seen to represent less than
5.5 per cent of the blood volume.

9. 25:3:35. Cat. Weight 2000 gm. Operation
as in Expt. 2.

28:3:35. Died in 72 hours.

Weight of undistended foot of ileum = 7.6 gm.

Weight of lowest occluded loop = 7.84 gm.

Therefore excess of blood and fluid in wall of lowest
obstructed loop = 0.2 gm.

But blood volume = 7.5 per cent. of 2000 = 150 cc.

Therefore excess of blood and fluid in wall of lowest
obstructed loop = $\frac{0.2 \times 100}{150}$ = 0.13 per cent. of
blood volume.

If this is corrected to represent the maximum possible

loss into the whole obstructed small intestine (length 5 feet), the loss is seen to be less than one per cent. of the blood volume.

N.B. In this series, it was attempted to measure the amount of blood loss into the lumen of the obstructed loop by estimating the amount of haemoglobin in the contents of the obstructed bowel. Gross difference in tint between bowel content and standard colorimeter control rendered this impossible. In no case, however, was there much blood obvious to the naked eye in the bowel content, and in four instances (1, 2, 8, 9) even the Benzidine reaction for blood was negative in that content. Death apparently occurs in simple low obstruction before blood loss into the lumen is considerable.

Table summarising Experiments 1 - 9.

No. of Expt.	Wt. of Cat.	Estimated blood vol.	Gain in weight of obstructed loop.	Expressed as percentage of B.V.	Corrected to show maximum loss into small intestine.
1	1500	112 cc.	0.9 gm.	0.8%	3 1/2%
2	2000	150 cc.	1.2 gm.	0.8%	3.2%
3	1500	113 cc.	1.1 gm.	1%	4%
4	3300	248 cc.	2.5 gm.	1%	5%
5	2300	Obstruction incomplete.			
6	2700	Ligature cut through: cat recovered.			
7	2900	218 cc.	0.2 gm.	0.1%	0.6%
8	2400	180 cc.	1.7 gm.	1%	5.5%
9	2000	150 cc.	0.2 gm.	0.13%	1%

Conclusion.

Loss of blood from the general circulation into the congested vessels of the wall of the affected bowel, is a negligible factor in simple intestinal occlusion.

10 - 16. Experiments to show the amount of blood loss from splanchnic congestion in closed loop ileal obstruction.

(see page 103)

10. 25:3:35. Cat. Weight 3100 gm. Ether anaesthesia (after two days starvation). Abdomen opened in mid line. One half of jejunum isolated as closed loop, by double division and inversion of ends by purse-string sutures. Lumen reconstituted around isolated loop by lateral anastomosis. Loop returned to abdomen.

27:3:35. Dead. No great vomiting. Closed loop greatly distended and cyanosed in parts, especially on antimesenteric border, but no great quantity of blood in lumen. Higher undistended half of small bowel collapsed and pale. Small amount of lightly blood-stained fluid in peritoneal cavity.

Weight of distended loop (emptied and cleaned as in Expt. 1) = 48 gm.

Weight of collapsed intestine (equal in length before operation) = 23 gm.

Therefore loss of blood and fluid from circulation into wall of closed loop = 25 gm.

But blood volume = (approx.) 7.5 per cent. of 3100
= 233 cc.

So fluid and blood loss = $\frac{25 \times 100}{233}$ i.e. less than
11 per cent. of blood volume.

If the whole small intestine were similarly treated, the maximum blood loss by splanchnic congestion would thus be less than 22% of the blood volume.

Experiments 11 to 16 were repetitions of Experiment 10, and the results in these and in Experiment 10 are summarised here for convenience, and to avoid repetition.*

Table on next page.

* In this series also, an attempt was made to determine by haemoglobin estimations the blood loss into the lumen of the closed loop. The colour of the content differed so greatly, however, from that of the standard solution that this was not practicable. In no case was there a gross amount even of changed blood in the bowel lumen, and in two instances - 11 and 15 - even the Benzidine test for the presence of blood in the loop contents, was negative.

[illegible]

Conclusion.

The loss of blood from the general circulation to the congested vessels of a closed intestinal loop is great enough to be important only when half or more of the whole jejunum-ileum is involved. The blood loss (as estimated by the gain in weight of the affected loop) may then represent from one-ninth to one-fifth of the total blood volume - a loss comparable to a serious, but not to a fatal, external haemorrhage. The blood loss into the wall of a closed loop of one quarter or less of the small intestine was trivial in this series - amounting in no case to more than one-thirtieth of the total blood volume.

17 - 21. Experiments to determine the blood lost from the general circulation into a loop of bowel excluded as a closed loop, and artificially distended to a point of venous congestion.

17. 11:12:34. Cat. Weight 3100 gm. Ether.
Loop of jejunum-ileum - one half exactly of small intestine - altered to a closed loop by double ligature, and distended by air to a pressure of 65 millimetres

of mercury - to the point, that is, of venous engorgement. Returned to the abdomen. 15 minutes later, abdomen reopened; distended loop opened (with prevention of bleeding), washed, and dried by cotton, and its weight compared with a healthy loop of equal length, similarly excised, washed and dried.

Weight of distended, congested loop = 105 gm.

Weight of healthy loop of equal length = 24 gm.

Therefore increase of blood and fluid in wall = 81 gm.

But blood volume = $7\frac{1}{2}$ per cent. of body weight (approx.)
= 233 cc.

Therefore blood loss into bowel wall = $\frac{81 \times 100}{233}$ i.e.

34 % of blood volume.

(In this experiment, unlike the preceding ones, the increase in weight of the obstructed bowel does not represent the total blood loss from the circulation, since in this and the succeeding experiments there was a considerable amount of blood present in the lumen. The results of this series, inaccurate as they for this reason are, are given below for completeness.)

18 to 21. As in Experiment 17, but various lengths of bowel used.

Summary of results of Experiments 17 to 21.

No. of Expt.	Fraction of small intestine distended	Wt. of distended loop	Wt. of healthy loop of equal length	Wt. of blood lost into bowel wall	Wt. of animal	Blood volume	Blood and fluid excess in bowel wall, expressed as percentage of blood volume.
17	one half	105	24	81	3100	233	34 per cent.
18	one half	85	21	64	2300	172	37 per cent.
19	one quarter	47.4	11.4	36	2800	210	17 per cent.
20	one quarter	41	14	27	3000	225	12 per cent.
21	one eighth	23.5	8.5	15	220	165	10 per cent.

Conclusions.

Artificial distention to give venous congestion in a closed loop composed of one half of the small intestine of the cat gives a blood loss from the general circulation comparable to a severe external haemorrhage. This artificial distention does not resemble any clinical condition in man, and in the dog, in closed loop obstruction without artificial distention, death occurs before a sufficient pressure is generated to cause venous engorgement of the degree induced in this

series (see Expts. 10 to 16). The series shows, however, how much blood can be accommodated in the acute congestion caused by a high intra-intestinal pressure.

22. Experiment to determine fluid loss into the bowel after release of an intestinal distention sufficient to cause anaemia of the bowel wall.

25:1:35. Cat. Weight 1800 gm. Eight inches of small intestine isolated by ligatures without reconstitution. Distended to the point of anaemia by saline, and kept so distended within abdomen for four hours. Distended loop then withdrawn and emptied of saline, returned to abdominal cavity, and kept there for fifteen minutes. After this period, animal killed, and distended loop, and a collapsed adjacent loop of equal length emptied, washed, and mucosa dried by cotton pull-through. The obstructed loop, white during its distention, was, fifteen minutes after collapse, darkly cyanosed.

Weight of 8-inch obstructed loop after collapse	=	18 gm.
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Weight of normal 8-inch loop	=	10 gm.
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Blood and fluid excess in cyanosed wall of
former = 8 gm.

But blood volume = $7\frac{1}{2}$ per cent. of 1800 = 140 cc.

Therefore blood loss in eight inches of bowel distended
for four hours and then collapsed for fifteen minutes

= 5.7 per cent. of blood volume.

But length of jejunum-ileum = 5 feet.

If the whole small intestine were similarly treated,
the blood loss might be expected to amount to $5.7 \times 7\frac{1}{2}$,
i.e., 43 per cent. of the blood volume.

Conclusion.

Since anaemia of the bowel does not occur clinically in a pure form, this experiment has only an academic interest. It demonstrates that the capillaries of the intestinal wall, paralysed by prolonged anaemia distention, can accommodate after release of that distention a considerable fraction of the total blood volume.

23 - 34. Experiments to demonstrate the blood
loss from the general circulation under con-
ditions of venous strangulation of the bowel.

23. 3:12:34. Cat. Weight 2800 gm. Ether.

Two and a half foot loop of intestine (equal to one

half of jejunum-ileum) withdrawn from abdomen: isolated by division of ends and invasion: before division, an equal amount of healthy small intestine marked off by seromuscular knots: lumen reconstituted around isolated loop by lateral anastomosis: isolated loop enclosed in balloon without constriction of neck: neck of balloon sewn to mesentery of loop: veins in mesentery ligated: arteries of loop not interfered with.

4:12:34. Mewing pitifully: lying on side: eyes clear but dry: no vomiting: taking drinks. Dead in twenty-four hours.

Peritoneal cavity contained 30 cc. dark thick fluid like pure blood, which had escaped through neck of balloon: balloon-loop plum coloured and distended with blood-stained fluid, but imperforated. Balloon contained 15 cc. of the same fluid as the peritoneal cavity.

Weight of balloon + gangrenous bowel + fluid in
balloon + fluid in peritoneal cavity = 170 gm.

Weight of balloon + 2½ ft. normal bowel = 60 gm.

Weight of blood and fluid lost into and from strangulated loop = 110 gm.

But blood volume of cat = (approx.) 7.5 per cent.
of 2800, i.e. 210.

Therefore fluid and blood lost = $\frac{110 \times 100}{210}$ = 52 per cent. of blood volume.

Balloon fluid and sero-muscular coat of bowel gave both aerobic and anaerobic organisms on culture.

24. 15:1:35. Cat. Weight 2800 gm. Ether. Whole jejunum-ileum strangulated in balloon, by a ligature tied around neck of balloon until pulsation in mesentery just perceptible through balloon wall. No reconstitution of lumen. Died in six hours.

Balloon distended by 45 cc. thick bloody fluid: 35 cc. of similar fluid in lumen: bowel unperforated, but black and swollen-walled. Bowel opened, washed, and mucosa dried by cotton.

Weight of balloon + fluid in bowel + bowel + fluid
in balloon = 185 gm.

Weight of balloon + equal length of jejunum-ileum
of cat of same weight and nutrition = 91 gm.

Therefore blood lost into and through wall of strangulated gut - 94 gm.

But blood volume = (approx.) 7.5 per cent. of 2800
= 210 cc.

Therefore fluid and blood lost by strangulation = 45 per cent. of blood volume.

25 - 34.

The cats used in these experiments were dealt with as was the cat in 24, except that smaller loops of bowel were isolated, the lumen was re-established by lateral anastomosis outside the balloon and the weight

of the balloon contents was compared with the weight of a healthy loop of bowel of similar length from the same animal. The results of the whole series 23 to 34 are tabulated below.

No. of Expt.	Fraction of jejunum strangu- lated	Wt. of balloon + con- tents	Wt. of balloon + normal loop of equal length	Wt. of blood lost	Estima- ted blood volume	Blood and fluid loss as percen- tage of blood volume	Duration of life
23	Whole	185	91	94	210	<u>45%</u>	Died in 6 hours
24	1/2	170	60	110	210	<u>52%</u>	Died in 24 hours
25	1/2	220	140	80	188	<u>43%</u>	Died in 24 hours
26	1/2	Died of peritonitis.			Ligature.		
27	1/2	"	"	"	"		
28	2/7	132	90	42	120	<u>35%</u>	Killed 18 hours
29	1/4	193	154	39	172	<u>23%</u>	Killed 24 hours
30	2/9	184	142	42	158	<u>27%</u>	Killed 18 hours
31	2/9	160	107	53	165	<u>32%</u>	Killed 18 hours
32	1/5	142	111	31	135	<u>23%</u>	Killed 18 hours
33	1/5	203	151	52	188	<u>28%</u>	Killed 24 hours
34	1/7	173	140	33	150	<u>22%</u>	Died (1) 20 hours

(1) In this animal, escape occurred of balloon fluid into the general peritoneal cavity, and accounted for its early death in spite of a slight blood loss.

Conclusions.

In venous strangulation of half or more of the small intestine gives early death, even though no absorption (peritoneal, venous, or lymphatic) occurs. The early death is explained by the enormous damming up of blood in the gut wall, and the passage of blood into lumen and peritoneal cavity. Even when much smaller loops are strangulated, the blood loss is still very serious (22-35 per cent. of the blood volume). The blood loss is roughly proportional to the length of loop strangulated. These experiments probably over-estimate the blood loss from strangulation as we know it clinically, since in the absence of the experimental balloon, some reabsorption of fluid and blood is probably attempted by the peritoneum.

35 - 37. Experiments showing the effect on the
blood pressure of an intestinal distention
which is followed by anaemia of the bowel.

35. Dog.

8:11:35. Intratracheal ether. Thoracic and abdominal sympathetic chain removed from 3rd thoracic to 3rd lumbar ganglia on right side through three incisions - one high intercostal, one low intercostal, one lumbar. Right vagus divided in thorax. Empyema followed, but ultimately recovery.

21:11:35. Same operation performed on left side.

1:3:35. Chloralose anaesthesia and intratracheal insufflation of air. Both vago-sympathetic trunks divided in neck. Right common carotid artery ligated. Manometer cannula inserted in left common carotid. Abdomen opened. Blood pressure allowed to stabilise. Small intestine distended as closed loop to 100 mm. mercury. Violent contraction of whole distended gut followed, bowel became anaemic, and the blood pressure, after an initial fall of a few millimetres, rose in less than one minute from 98 to 146 mm. of mercury (Fig. 1, page 71). Deflation four minutes later was followed in one minute by a fall of blood pressure to the original level.

36. Dog.

9:2:35. Left sympathectomy and vagotomy as above.

22:11:35. Right sympathectomy and vagotomy as above.

1:3:35. Chloralose anaesthesia: intratracheal insufflation of air. Both vago-sympathetic trunks divided in neck. Right common carotid artery ligated. Manometer cannula inserted in left common carotid. Abdomen opened. Whole small intestine isolated as closed loop. Air inflation to a pressure of 100 mm. of mercury was followed by strong contraction of the bowel, and anaemia of its wall. The blood pressure rose from 102 mm. of mercury to 130, after an initial fall to 92.

37. Dog.

29:2:35. Intratracheal ether. Manometer cannula in left common carotid. Right common carotid ligated. Both vago-sympathetic trunks left intact. Abdomen opened. Superior mesenteric artery stripped of its nerve plexus (to exclude afferent stimuli from bowel). Whole small intestine, when distended as closed loop, to a pressure of 90 mm. Hg., contracts and pales, and blood pressure rises from 68 mm. of

mercury to 80 mm. in fifty seconds.

38. Intact dog. Intratracheal ether. Manometer cannula in right carotid artery. Abdomen opened. Whole small intestine isolated as closed loops. Blood pressure allowed to reach steady level. Intestine distended by air to pressure of 80 mm. of mercury. Colour rapidly turned purple. Blood pressure fell from 122 mm. of mercury to 106 mm. in fifteen seconds.

39. Intact dog.

28:3:35. Intravenous amytol. Manometer cannula in right carotid artery. Abdomen opened. Whole small intestine isolated as closed loop. Blood pressure allowed to stabilise. Bowel, distended now with air to a pressure of 90 mm. of mercury, became cyanosed, and blood pressure fell from 120 mm. of mercury to 102.

40. Dog.

28:3:35. Intratracheal ether. Manometer cannula inserted in right carotid artery. Left carotid ligated. Both vago-sympathetic trunks divided in neck. Abdomen opened. Whole small intestine isolated as closed loop. Blood pressure allowed to

stabilise. Intestine now distended with air to a pressure of 120 mm. Hg. Bowel becomes congested, and blood pressure falls from 116 to 104 mm. of mercury in twenty seconds.

41. Dog.

26:2:35. Intratracheal ether. Manometer cannula inserted in right carotid artery. Left common carotid ligated. Both vago-sympathetic trunks divided in neck. Abdomen opened. Whole small intestine isolated as closed loop. Blood pressure permitted to stabilise.

(1) Intestine inflated with air to a pressure of 62 mm. of mercury. During half a minute, the bowel contracts vigorously, becomes abnormally pale, and the blood pressure rises to 172, to fall at once to 144 mm. of mercury as contraction lessens, and cyanosis comes on.

(2) Deflation of intestine five minutes later followed by a return of the colour of the bowel to normal, and a rise of blood pressure to 172 (Fig. 5 page 75) (compare with 60).

42. Cat.

27:3:35. Intravenous sodium amytal and intratracheal insufflation of air. Manometer cannula in

right carotid. Left carotid ligated. Both vago-sympathetic trunks divided in neck. Abdomen opened. Whole small intestine isolated as closed loop. Blood pressure allowed to stabilise.

(1) Intestine distended with air to pressure of 80 mm. of mercury, and kept so distended for five minutes, with bowel wall in congestion. On release of distention at the end of that period, the bowel returned to its normal pale colour, and the blood pressure rose from 134 to 184 mm. of mercury (Fig. 3 page 74).

(2) On re-inflation of the gut to the same level, the blood pressure fell once more to 122, in one minute and a half.

43. Dog.

27:3:35. Intravenous sodium amytal and intra-tracheal insufflation of air. Carotids and vago-sympathetic trunks dealt with as in previous experiment, and small intestine similarly distended, but denervated by division of superior mesenteric nerve plexus.

(1) Upon distention by air to 90 mm. of mercury, the bowel became cyanosed, and the blood pressure fell in forty seconds from 124 to 88 mm. of mercury, only

to rise almost to its original level. The intestinal wall was congested.

(2) Distention released after two minutes. Bowel wall regained its normal pallor, and the blood pressure, rose from 100 to 130 in forty seconds.

44. Cat.

27:3:35. Sodium amytal: prepared as in previous experiment.

(1) Venous congestion of whole small intestine induced by raising intra-intestinal pressure to 90 mm., and maintained for five minutes. Upon release of the distention, rise in blood pressure from 102 mm. of mercury to 204 in two and a half minutes. The colour of the bowel returned to normal.

(2) Redistention of jejunum-ileum to 90 mm. of mercury was followed by congestion again, and by a fall of blood pressure from 166 to 102 mm. of mercury in three and a half minutes, after a transient initial rise (Fig. 2, page 73).

45. Dog.

28:3:35. Intratracheal ether. Abdomen opened. Whole small intestine isolated as closed loop and returned to abdomen, distended in cyanosis by air at

a pressure of 100 mm. of mercury and denervated by division of superior mesenteric plexus.

Four hours later, intratracheal ether again. Abdomen opened. Manometer cannula inserted in right carotid artery. Left carotid ligated. Both vago-sympathetic trunks divided in neck. Blood pressure permitted to stabilise. The still-cyanosed and distended bowel now opened and collapsed rapidly. Blood pressure rose from 96 mm. of mercury to 124 as colour returned to normal pallor (Fig. 4, page 75). Reinduction of cyanotic distention after five minutes gave a new fall in blood pressure.

46. Dog.

29:3:35. Repetition of previous experiment, but intra-intestinal pressure of 120 mm., with cyanosis here maintained for eight hours. Upon release, return of bowel colour to normal, and rise of blood pressure from 132 to 176 mm. of mercury in one minute.

47. Dog.

29:3:35. Repetition of previous experiment but bowel kept within abdomen, in cyanosis, at an intra-intestinal pressure of 90 mm. of mercury, for seven hours. Upon release of distention, rise in blood

pressure from 142 to 164 in 90 seconds.

48. Cat.

30:3:35. Repetition of previous experiment, but intra-intestinal pressure of 80 mm. of mercury here maintained for five hours. Upon release of distention, return of bowel to normal colour, and rise in blood pressure from 116 to 184, in two minutes.

49 - 53. Release of an intestinal distention of a degree to cause cyanosis, but of medium duration. Effect on blood pressure.

49. Dog.

14:3:35. 8.30 a.m. Ether. Abdomen opened. Whole small intestine isolated as closed loop and denervated by division of superior mesenteric nerve plexus. Intestine distended by air inflation to a pressure of 90 mm. of mercury, and returned to abdomen in deep cyanosis.

2.30 p.m. (6 hours later). Intratracheal ether. Manometer cannula tied in right common carotid artery. Left common carotid ligated. Both vago-sympathetic trunks divided in neck. Abdomen open. Small intestine still distended and cyanosed. Blood pressure allowed to stabilise. Intestine quickly opened and

collapsed. In two minutes the normal pale colour of the gut had returned. In three minutes the blood pressure, instead of rising as would be expected from the increased return of venous blood from the bowel to the right heart, had fallen from 194 mm. of mercury to 139, stabilising at that last level (Fig. 7, page 77).

50. Dog.

5:4:35. 3 p.m. Ether. Abdomen opened. Whole small intestine treated exactly as in previous experiment, but returned distended to abdomen and left there for seventeen hours before second operation. On release of distention, the bowel rapidly regained its normal colour. The blood pressure showed a transient rise (30 seconds) from 102 to 112 mm. of mercury, a fall then to 80 in the next half-minute, and a steady fall thereafter to 24 mm. seven and a quarter minutes after release of the obstruction. At this point of time, death occurred. (Fig. 11, page 79)

51. Dog. 9:4:34. 3 p.m. Closed loop of whole small intestine isolated, denervated, distended and returned to abdomen as in previous animal.

10:4:34. 9 a.m. (18 hours later). Intratracheal ether. Second operation as in previous animal. On

release of obstruction, colour of bowel returned to normal in six minutes, and blood pressure fell steadily from 167 mm. of mercury to stabilise at 135 four minutes after collapse of bowel (Fig. 9, page 78). The respiratory movements of this dog after the release of distention manifested a slow gasping rhythm, slower than and quite asynchronous with the artificial respiration via the intratracheal tube.

52. Dog.

25:1:35. Intratracheal ether. Right splanchnic and vagus nerves divided within chest by low intercostal incision.

21:2:35. Intratracheal ether. Left splanchnic and vagus nerves divided within chest by low intercostal incision. Empyema, but recovered after four weeks external drainage.

8:3:35. 8 p.m. Intravenous sodium amytal. Abdomen opened. Whole small intestine isolated, distended to 40 mm. of mercury (mild cyanosis). Returned to abdomen.

9:3:35. 2 p.m. (18 hours later) Intratracheal ether. Manometer cannula to right carotid: left carotid clamped: one inch of each vago-sympathetic trunk excised in neck. Abdomen reopened. Blood

pressure allowed to stabilise. Intestine (still mildly congested) deflated. Fall in blood pressure from 170 to 148 in first half-minute, rising rapidly to 158, and falling again to reach 114 in nine minutes (Fig. 10, page 78.)

53. Intact Dog.

5:3:35. 8 p.m. Sodium amytal. Abdomen opened and whole small intestine distended as a closed loop to 80 mm. Hg. Returned, cyanosed, to abdomen.

6:3:35. 8 a.m. (12 hours later). Manometer cannula inserted in left common carotid. Right common carotid and vago-sympathetics not interfered with. Abdomen re-opened. Blood pressure allowed to stabilise. Intestine rapidly deflated. Fall in blood pressure from 98 to 75 in sixty seconds as intestine collapses and returns to its normal pale colour. It is important to notice here that the blood pressure is much lower after the distention than in the previous animals, where the bowel had been denervated, but that, in the presence here of the path of the vago-pressor reflex, the fall in pressure after deflation of the gut is milder than in the previous animals, where the vago-sympathetic trunks were interrupted (Fig. 8, page 77).

54 - 55. Effect on blood pressure of release
of prolonged distention of bowel.

54. Dog.

7:3:35. Intratracheal ether. Abdomen opened. Whole small intestine isolated as closed loop, distended to 90 mm. of mercury with air, denervated by division of superior mesenteric plexus, and returned, congested, to abdomen.

8:3:35 (21 hours later). Intratracheal ether. Cannula inserted in right common carotid. Left common carotid ligated. Both vago-sympathetic trunks divided in neck. Deflation of the bowel was followed by no change in the colour of the deeply cyanosed bowel - pulsation remained absent in the mesentery and extensive thrombosis had obviously occurred in the bowel wall. No alteration in blood pressure followed deflation of the bowel. The animal was almost moribund and the blood pressure only amounted to 76 mm. of mercury.

55. Dog.

8:3:35. Repetition of previous experiment, and identical with it, except that the increased intra-intestinal pressure was here maintained for seventeen

hours. On release of the distention, the plum coloured bowel again failed to change colour, and was obviously devitalised, thrombosis being apparent in its veins. Here again no alteration in blood pressure followed deflation. This animal too, with a blood pressure of only 60 millimetres of mercury, was at the time of deflation, weak to the point of death.

56. Effect of obstruction and release of the superior mesenteric vein. For comparison with Experiments 38 to 48.

Dog. 28:3:35. Intratracheal ether. Cannula inserted in left common carotid: right common carotid ligated: both vago-sympathetic trunks divided in neck. Clamping of the superior mesenteric vein was followed immediately by a fall in blood pressure from 90 to 66 mm. of mercury. Release of the clamp was followed by a rise of blood pressure again to the original level. The effect is the same as when venous congestion is induced by inflation, and deflation follows shortly (Fig. 6, page 76).

Table Summarising Results of Experi-
ments 35 to 44.

No. of Expt.	Intra-intestinal pressure induced	Resultant change in bowel circulation	Alteration in blood pressure.
35	100 mm. Hg.	Anaemia	+ 48 mm. Hg.
36	100 mm. Hg.	Anaemia	+ 28 mm. Hg.
37	90 mm. Hg.	Anaemia	+ 12 mm. Hg.
38	80 mm. Hg.	Cyanosis	- 16 mm. Hg.
39	90 mm. Hg.	Cyanosis	- 18 mm. Hg.
40	120 mm. Hg.	Cyanosis	- 12 mm. Hg.
41 (1)	62 mm. Hg.	Cyanosis	- 28 mm. Hg.
42 (2)	80 mm. Hg.	Cyanosis	- 62 mm. Hg.
43 (1)	90 mm. Hg.	Cyanosis	- 36 mm. Hg.
44 (2)	90 mm. Hg.	Cyanosis	- 64 mm. Hg.
56	Superior mesenteric vein clamped.	Cyanosis	- 24 mm. Hg.

Conclusion.

The effect on the blood pressure of an increased intra-intestinal pressure depends on whether the distention of the gut induces anaemia or congestion in the bowel wall. If the latter, the blood pressure falls, if the former, the blood pressure rises.

Table Summarising Results of Experiments 41 to 60
showing time factor in effect of release of
intestinal distention on blood pressure.

Expt.	I.I.P. In- duced	Animal	Afferent paths from heart in- terrupted	Afferent paths from gut inter- rupted	Duration of Distention	Change in bowel cir- culation	Alter- ation in B.P.	Expla- nation
41	62	Dog	Yes	No	5 minutes	Return to normal	+ 28	Increased return of nervous blood to heart.
42	80	Cat	Yes	No	5 minutes	"	+ 50	
43	90	Dog	Yes	Yes	2 minutes	"	+ 30	
44	90	Cat	Yes	Yes	5 minutes	"	+ 102	
45	100	Dog	Yes	Yes	4 hours	"	+ 28	
46	120	Dog	Yes	Yes	8 hours	"	+ 44	
47	90	Dog	Yes	Yes	7 hours	"	+ 22	
48	80	Cat	Yes	Yes	5 hours	"	+ 68	
56	-	Dog	Release of ligation		Superior mesenteric vein	"	+ 24	
49	90	Dog	Yes	Yes	6 hours	Return to normal	- 55	? return of depres- sor substance in blood from intes- tine.
50	90	Dog	Yes	Yes	17 hours	"	- 78 (death)	
51	90	Dog	Yes	Yes	18 hours	"	- 32	
52	40	Dog	Yes	Yes	18 hours	"	- 56	
53	80	Dog	No	No	12 hours	"	- 23	
54	90	Dog	Yes	Yes	21 hours	Remained cyanosed	No change	Thrombo- sis in intesti- nal veins
55	90	Dog	Yes	Yes	17 hours	"	"	

Conclusion.

Release of an intestinal distention, of cyanotic degree, and present for six to eight hours or less, is followed by a rise in blood pressure, consequent upon the increased return of blood to the right heart. Release of a similar distention of more than six to eight hours, but less than seventeen or eighteen hours, gives an unexpected fall in pressure and suggests the return of a depressor substance in the blood held up during the distention period, in the intestinal veins. After seventeen or eighteen hours, the veins in the intestinal wall have thrombosed, and blood can return from them, neither to augment the circulating volume, nor to carry any depressor substance into the general circulation: the problem in such a long-distended bowel is one not of obstruction, but of strangulation.

57 - 67. Experiments to show presence of a depressor substance in the portal blood of a dog after release of a twelve-hour intestinal distention.

57 & 58. Normal dogs. Ether anaesthesia. Whole small intestine doubly ligated as closed loop. Inflated with air to a pressure of 70 or 80 mm. of mercury, and returned to abdomen. Twelve hours later,

abdomen reopened, intestine rapidly collapsed, portal vein canalised and blood drained into citrate flask during deflation of bowel. The gut in these two animals failed to regain its normal colour on deflation, the intestinal and mesenteric veins being obviously thrombosed. The yield of portal blood was small, and neither the citrated blood, nor the plasma collected by centrifugalisation, gave a fall of blood pressure when injected in quantities of 15 to 30 cc. intravenously in other dogs.

59. Dog. Treated as in 57 and 58; although the bowel here returned to its normal pallor after deflation, and the yield of portal blood was considerable in amount (250 cc.), no fall of blood pressure followed its intravenous injection into another dog.

60, 61, 62 & 63. In these four dogs, treated in the same manner as 57 and 58, the intestine regained its normal colour, and 250 to 350 cc. of citrated portal blood was collected from each. The specimens of blood and of plasma from these four animals, when injected intravenously in doses of 15 cc., gave depression of the blood pressure of the injected animal by 40 to 60 mm. of mercury in each case. In one case

there was a definite fall in the blood pressure of the injected dog after intravenous injection of as little as 3 cc. of the portal blood or plasma drawn after relief of distention in the donor dog (Fig. 12 & 13 pp. 85 & 86).

64, 65, 66 & 67. The citrated portal blood, and portal plasma, from four normal unobstructed dogs failed to give any depression of the blood pressure after intravenous injection, even when allowed to stand on ice for seventy-two hours (Fig. 14, page 86).

Conclusions.

There is a depressor substance present in the portal blood of a dog immediately after release of a distention of the intestine sufficient to cause cyanosis, and maintained for a period of twelve hours.

The Chemical Properties of the Depressor Substance Present in the Portal Blood of a Dog after relief of Intestinal Distention.

(1) Protein fractionation.

The following protein fractionation was performed on each of the four specimens of portal blood from dogs 60 to 63:-

(A) To 45cc. of blood was added 23 cc. of saturated ammonium sulphate solution. The blood thus one-third saturated with ammonium sulphate was filtered, and the chocolate precipitate, representing the euglobulin fraction of the blood protein, dissolved in 10 cc. saline, and dialysed in a celloidin tube against saline for three days, with nine changes of dialysate.

(B) To the filtrate from (A), was added an equal volume of saturated ammonium sulphate, and filtration again performed. The collected precipitate was dissolved in 10 cc. of saline, freed from sulphate by the same dialysis as in (A). This saline solution contained the pseudo-globulin fraction of the blood protein.

(C) To the filtrate from (B) was added an excess of crystalline ammonium sulphate, to give full saturation with the salt. The resultant precipitate, collected, dissolved in 10 cc. saline, and freed from sulphate by dialysis just as in (A) and (B), consisted of the albumen fraction of the blood.

(D) The filtrate from (C) was dialysed through celloidin against water, and the clear fluid obtained assumed to contain any proteose or peptone present in portal blood.

68 - 84. The euglobulin, pseudoglobulin, albumen and proteose-peptone precipitation fractions from the depressor portal blood of dogs 60 to 63 were injected intravenously into normal dogs in doses corresponding to 15 and 30 cc. of the original portal blood. None of these exercised any effect on the blood pressure of the injected dog, except in the case of the proteose peptone fraction of dog 43, which gave a pronounced fall in blood pressure. This effect was found to be due to a residuum of ammonium sulphate left by inadequate dialysis. Further dialysis of this filtrate removed its depressor properties.

It can accordingly be assumed that the depressor substance in the portal blood of a dog after release of an intestinal distention is non-protein and diffusible.

(2) Non-Protein Extract of Portal Blood from dogs

60 to 63.

To 50 cc. of the plasma of each specimen of actively depressor portal blood of dogs 60 to 63 was added 3.75 gm. of trichloroacetic acid. This mixture was kept on ice for twenty-four hours, and filtered. The filtrate, after five extractions with ether in a separating flask to free it of trichloroacetic acid,

represented the non-protein, and non-lipoid elements in the portal plasma.

84 - 87. Each of these non-protein fractions of the portal serum of dogs after relief of a twelve-hour venous distention of the gut, gave a noticeable fall in the pressure of the etherised dog in doses corresponding to as little as 6 cc. of the original plasma, or 14 cc. of the original portal blood (Figs. 15 & 16, p.p. 89 & 90).

88. Non-protein fractions prepared similarly from the portal serum of four normal unobstructed dogs gave no depression of blood pressure in the etherised dog when injected intravenously in doses corresponding to 15 to 30 cc. of the original portal blood.

89. Doses of filtrate corresponding to 15 cc. of the original portal blood of dogs 60 to 63 were boiled for 20 minutes. Intravenous injection of the boiled filtrate still gave a slight but perceptible fall in blood pressure.

90. A fraction of the filtrate from dogs 60 and 63, of known depressor effect, was boiled for twenty minutes after the addition of one part of concentrated

hydrochloric to five parts of filtrate and then neutralised by the addition of sodium hydroxide. The depressor effect on the blood pressure of the etherised dog persisted (Fig. 17, page 91).

91. One part of sodium hydroxide was added to five parts of the active filtrate from dog 52, the mixture boiled for twenty minutes, and neutralised by the addition of normal hydrochloric acid. Intravenous injection of the filtrate, hydrolysed in this way, in doses corresponding to 20 cc. of the original portal blood, had no effect on the blood pressure of the etherised dog.

92. A portion of the active extract from dog 53 was deaminised by acid boiling after addition of sodium nitrite. Intravenous injection of the deaminised filtrate, in doses corresponding to 15 cc. of the original plasma was followed by a marked fall in blood pressure in the injected etherised dog.

93. To the active filtrate of dog 53, alcohol was added to a concentration of 80 per cent., and the alcoholic solution filtered. To the filtrate, three volumes of acetone were added, and filtration again performed. The precipitate (invisible) from the

second filtration was dissolved from the filter paper in water. It had no depressor effect on the blood pressure of the etherised dog.

94. The Pauly (diazo) reaction for histamine was performed on the filtrate with a negative result.

Summary of Experiments 68 to 94.

The depressor principle apparently present in the portal serum of a dog after relief of an intestinal distention of twelve hours duration is non-protein and diffusible. It is not precipitated by saturation with ammonium sulphate or by trichloroacetic acid. It passes easily through a celloidin membrane. It is destroyed by alkaline hydrolysis, but its activity persists in some degree at least after neutral boiling, acid hydrolysis, and deamination. It is not precipitated by acetone from alcoholic solution. The Pauly reaction for histamine is negative.

95 - 104. Experiments to Determine the
Specific Biological Activities of the
Depressor Substance Present in Portal
Blood after the Relief of Intestinal
Distention.

95 - 98. Amounts of the active filtrate from each of the four dogs 60 to 63 corresponding to 6 cc. of portal serum (14 cc. portal blood) were injected intravenously into an etherised rabbit. Each of these injections was followed by a substantial depression of the rabbit's blood pressure.

99. This depressor effect on the blood pressure of the rabbit persisted after previous atropinisation.

100, 101, 102, 103 & 104. The effect of active filtrate was tested on virgin guinea pig uterus, rabbit intestine, eserinated leech muscle, jejunum of cat, and rectus abdominis of frog, being added to the water bath in which these were each suspended in concentrations as great as one part of blood to forty parts of saline in each case. No activity was detected.

105 - 110. Experiments to determine the Importance of Peritoneal Absorption in Closed loop Obstruction.

105. Cat. Ether anaesthesia. Abdomen opened. Loop of lower ileum separated, ligated at each end, and ligated ends invaginated. Lumen re-constituted by end-to-end anastomosis. Closed loop placed in rubber balloon. Neck of balloon stitched closely to mesentery of loop, with careful avoidance of injury to the mesenteric vessels or constriction of them. Omentum laid round neck of balloon, and closely sutured to balloon and to mesentery. After this closure, the air in the balloon could not be expelled by pressure. Abdominal contents and balloon with closed loop returned to peritoneal cavity, and abdomen closed.

Twenty hours later. Animal dead. Closure of neck of balloon still air-tight. No fluid in general peritoneal cavity. Small amount of yellow fluid in balloon. Closed loop in balloon mildly congested and distended but not obviously devitalised. Contents of closed loop pale brown in colour - no obvious blood.

106. As 105, but twelve-inch loop of jejunum

isolated similarly. Death in twenty hours. Same post-mortem findings.

107. As 105, but twelve-inch jejuno-ileal loop isolated. Death in twelve hours. Same post-mortem findings as in 105.

108. As 105. Twelve-inch ileal loop isolated. Same post-mortem appearances as in 105.

109. As 105, but ten-inch jejunal loop isolated in balloon. Death in eighteen hours. No fluid in general peritoneal cavity, but several cubic centimetres of blood-stained fluid in balloon. Closed loop in balloon greatly distended, and deeply cyanosed with patches of gangrene on the anti-mesenteric border.

110. As 109 but twelve-inch ileal loop isolated. Same post-mortem appearances as in 109.

111 - 128. Experiments to show the Toxicity of the Peritoneal Transudate of Strangulated Intestinal Loops, and its Relation to the Presence of Bacteria in the Transudate and in the Wall of the Strangulated Bowel.

Seventeen cats had one foot or more of their

small intestine subjected to venous strangulation in a rubber balloon within the peritoneal cavity. They died or were killed after periods varying from six to thirty hours. The fluid collected from the balloons was tested for toxicity by intraperitoneal injection into other animals. Cultures were made of the sero-muscular coat of the strangulated bowel, and the transudate itself. The results are tabulated below.

No. of Expt.	Length of bowel strangulated	Length of survival period	Result of intra-peritoneal injection of balloon fluid into other animals	Cultures of sero-muscular coat	Cultures of balloon fluid
111 (= 23)	Whole small intestine	Died in 6 hours	Whole amount non-toxic to guinea pig	Sterile	Sterile
112	One foot ileum	Killed in 8 hours	" " "	"	"
113	One foot jejunum	Killed in 10 hours	" " "	"	"
114	One foot ileum	Killed in 12 hours	" " "	"	"
115	One foot jejunum	Killed in 15 hours	" " "	"	"
116 (= 30)	One foot ileum	Killed in 18 hours	" " "	"	"
117 (= 32)	One foot jejunum	Killed in 18 hours	" " "	"	"
118 (= 28)	One foot ileum	Killed in 18 hours	" " "	"	"
119 (= 25)	Two and a half feet	Died in 24 hours	" " "	"	"
120	One foot	Killed in 30 hours	Whole amount killed cat in 8 hours (1,2,3,5)	Aerobes and Anaerobes	Aerobes and Anaerobes
121 (= 31)	One foot	Killed in 18 hours	5 cc. killed guinea pig in 8 hours (1,2,3,4) 2 cc. killed mouse in 2 hours	Aerobes and Anaerobes	Sterile
122 (= 24)	Two and a half feet	Died in 24 hours	2 cc. killed guinea pig in 4 hours (1)	Aerobes and Anaerobes	Aerobes and Anaerobes
124 (= 29)	One foot ileum	Killed in 24 hours	5 cc. killed guinea pig in 7 hours (1,2,3)	Aerobes and Anaerobes	Aerobes and Anaerobes
125 (= 34)	9 inches ileum	Died in 20 hours	5 cc. killed guinea pig in 6 hours (1,2,5) 2 cc. killed mouse in 2 hours	Aerobes and Anaerobes	Aerobes and Anaerobes
126 (= 33)	One foot ileum	Killed in 24 hours	5 cc. killed guinea pig in 8 hours (1,2,3,4)	Aerobes and Anaerobes	Aerobes and Anaerobes
127	One foot ileum	Killed in 20 hours	5 cc. killed guinea pig in 6 hours (1,2)	Aerobes and Anaerobes	Sterile
128	One foot ileum	Killed in 27 hours	4 cc. killed guinea pig in 5 hours (1,3,4,6)	Aerobes and Anaerobes	Aerobes and Anaerobes

1. Apathy, weakness, increased respiratory rate before death. P.M. no peritonitis.
2. P.M. - Marked congestion of liver and spleen.
3. Spastic seizures of hind limbs before death.
4. Intense respiratory embarrassment before death. P.M. Emphysema.
5. Velvety red congestion of duodenum and upper jejunum.
6. P.M. Subendocardial haemorrhages.

129 - 133. The Bacterial Origin of the Toxaemia
from Strangulated Intestinal Loops of Medium
Length.

Five guinea pigs were subjected to aseptic laparotomy at periods varying from eight to ninety-six hours after death. Whole small intestine was ligated at both ends in each case, and the superior mesenteric vessels separately tied - the vein a short time before the artery. Whole small intestine then placed with aseptic precautions in peritoneal cavity of a cat. Cultures were made of the contents of the guinea pig bowel before transposition. The condition in the cat now closely resembled strangulation of a bowel loop with its blood supply completely cut off, but with peritoneal absorption still possible. The difference in species of strangulated gut and host did not lessen the risk of death from toxaemia. The results are summarised in the following table:-

No. of Expt.	Age of guinea pig donor	Culture of content of guinea pig bowel	Effect of transplant on cat host
129	8 hours	Sterile	No ill effects: indefinite survival.
130	32 "	Sterile	" " " "
131	56 "	Sterile	" " " "
132	72 "	Aerobes & anaerobes	Died 24 hours. Transplanted bowel distended. No peritonitis.
133	96 "	Aerobes & anaerobes	Died 20 hours. do. do.

134. The Chemical Nature of the Toxic Elements of the Transudate from Strangulated Intestine.

50 cc. of transudate were collected 24 hours after strangulation in balloons of five loops of cat small intestine. The specimen from each of these loops was found to be fatal when injected in quantities of 2 cc. intraperitoneally in guinea pigs. The transudate was filtered and subjected to the following chemical separation:-

(a) To 50 cc. of transudate, 25 cc. of saturated ammonium sulphate was added; the precipitate,

collected by filtration, was dissolved in 50 cc. physiological saline, and dialysed in a celloidin tube against physiological saline in an ice chamber for four days, with three daily changes of dialysate. The resultant saline solution contained the euglobulin fraction of the toxic balloon fluid.

(b) To the filtrate from (a) was added a further 25 cc. of saturated ammonium sulphate, to give half-saturation with that salt. Filtration was performed and the precipitated globulins dissolved, while still damp, in 50 cc. physiological saline. The globulin solution was freed of ammonium sulphate by celloidin dialysis against saline solution, for four days, with three daily changes of dialysate.

(c) The filtrate from (b) was saturated by the addition of an excess of crystalline ammonium sulphate. The precipitated albumins (and with them any proteose present in the transudate) were collected by filtration, dissolved in 50 cc. of physiological saline, and freed of ammonium sulphate by four days celloidin dialysis against saline.

(d) The filtrate from (c), containing any peptones in the original balloon transudate, was freed of ammonium sulphate, and of diffusible constituents of

the original fluid, by four days celloidin dialysis against distilled water. The resultant fluid was reduced by vacuum evaporation to a volume of 50 cc.

Injection experiments (intraperitoneal injections in guinea pigs).

A. Euglobulin (10 cc. solution = euglobulin content of the transudate of a single 24-hour strangulated loop).

- (1) 0.2 cc. euglobulin solution gave no symptoms.
- (2) 0.5 cc. gave no symptoms.
- (3) 0.8 cc. " " "
- (4) 1 cc. " " "
- (5) 0.5 cc. gave torpor and spastic convulsions for a few hours, with recovery.
- (6) 0.5 cc. do. do. do.
- (7) 1 cc. do. do. do.
- (8) 0.5 cc. followed by death in 8 hours.
- (9) 0.5 cc. " " " " 8 "
- (10) 0.8 cc. " " " " 6 "
- (11) 1 cc. " " " " 4 "
- (12) 1 cc. " " " " 7 "
- (13) 3 cc. " " " " 6 "
- (14) 3 cc. " " " " 5 "
- (15) 5 cc. " " " " 4 "
- (16) 5 cc. " " " " 8 "
- (17) 10 cc. " " " " 4 "

In the animals dying after euglobulin injection, death was preceded usually by spastic seizures of the limbs: post-mortem the liver and spleen were congested: in one animal⁽¹⁷⁾ there was in addition a patchy congestion of the mucosa of the small intestine. In a minority, there was haemolytic staining of the endocardium and aortic intima.

(18) Four mice, each injected intraperitoneally with 3 cc. of euglobulin solution, died within four hours.

(19) Control experiments:- six guinea pigs, each injected intraperitoneally with the euglobulin content of 20 cc. of normal dog portal blood, showed no ill effects.

(20) Control Experiment. Four guinea pigs, each injected with the total euglobulin content of a balloon in which cat bowel had been strangulated for less than 12 hours, showed no ill effects.

B. Globulin fraction (10 cc. of solution - globulin fraction of the transudate from a single 24-hour strangulated loop).

(1) 10 cc. injected intraperitoneally in a guinea pig gave no ill effects.

(2) 10 cc. do. do. do.

(3) 10 cc. do. do. do.

(4) 10 cc. do. do. do.

C. Albumin-proteose fraction (10 cc. of solution = albumin fraction of the transudate from a single cat loop).

(1) 10 cc. injected intraperitoneally in a guinea pig gave no ill effects.

(2) 10 cc. do. do. do.

(3) 10 cc. do. do. do.

(4) 10 cc. do. do. do.

D. Peptone fraction.

(1) 10 cc. injected intraperitoneally in a guinea pig gave no ill effects.

(2) 10 cc. do. do. do.

(3) 10 cc. do. do. do.

(4) 10 cc. do. do. do.

135. 10 cc. of toxic euglobulin solution (134, A) were boiled at 97%: a coagulum formed from which 4 cc. of clear fluid was expressed. This, when injected intraperitoneally in a guinea pig, failed to show any toxic effects.

136. The Protein-Free Extract of the Transudate from 24-hour Strangulated loops of cat intestine.

This was prepared by adding to the transudate of

seven loops of cat intestine strangulated 24 hours in balloons; 64 cc. of transudate were collected. To this was added 6 cc. of trichloroacetic acid. The mixture was shaken, allowed to stand for two hours, filtered, and the filtrate extracted four or five times with ether, to remove the acid. 10 cc. of this extract thus corresponded to the average non-protein content of the transudate from a single loop.

Injections of Protein-free Extract of Balloon

Transudate.

- | | | | |
|------|---------|--|--|
| (1) | 2 cc. | injected intraperitoneally in a young guinea pig gave death in | 30 minutes. |
| (2) | 3 cc. | do. do. do. | 45 " |
| (3) | 4 cc. | do. do. do. | 15 " |
| (4) | 5 cc. | do. do. do. | 60 " |
| (5) | 6 cc. | do. do. do. | 12 " |
| (6) | 8 cc. | do. do. do. | 15 " |
| (7) | 10 cc. | do. do. do. | 7 " |
| (8) | 10 cc. | do. do. do. | 2 " |
| (9) | 1 cc. | do. | was followed by no ill effects. |
| (10) | 0.5 cc. | do. | was followed by only slight respiratory embarrassment. |
| (11) | 0.2 cc. | do. | was followed by no ill effects. |
| (12) | 0.2 cc. | do. | " " " " " " |

All the dying animals suffered from considerable

respiratory embarrassment.

(13) Control Experiments. Four guinea pigs injected intraperitoneally with 5 cc. of a similarly prepared protein-free extract of normal cat blood presented no symptoms.

(14) Control Experiments. Four guinea pigs injected intraperitoneally with 5 cc. of a similarly prepared protein-free extract of the balloon fluid from cat loops strangulated for less than twelve hours, presented no symptoms of intoxication.

137. The Biological Activity of the Euglobulin
Fraction of Balloon Fluid from 24-hour
Strangulated loops.

(1) 3 cc. euglobulin solution (134, A) injected intravenously in a dog under intratracheal anaesthesia gave a transient fall in blood pressure (measured by carotid cannula mercury manometer) from 140 mm. to 95 mm., followed by a rapid rise to the original level.

(2) 3 cc. euglobulin solution (134, A) injected intravenously in a dog under chloralose anaesthesia and intratracheal insufflation of air, gave a few wild variations in blood pressure, with a rise from 110 mm. of mercury to 130 mm., and one minute's apnoea

before stabilising at the original level.

(3) 3 cc. euglobulin solution (134, A) gave a rise in pressure from 130 mm. of mercury to 160 mm., which was maintained over a period of several minutes before returning slowly to 130 again.

(4), (5), (6). 1 cc., 3 cc. & 5 cc. of euglobulin solution (134, A) injected intravenously in three dogs, gave no change in the blood pressure.

(7), (8), (9), (10). $1/5$ cc., $1/2$ cc., 1 cc. and 2 cc. of euglobulin solution (134, A) injected intravenously in the etherised rabbit, had no effect on the blood pressure.

138. The Biological Activity of the Protein-free Filtrate of Balloon Fluid from 24-hour Strangulated Loops.

(1) 5 cc. of protein-free filtrate (135) of the transudate from a loop of cat intestine strangulated in a balloon for 24 hours, was injected intravenously in a dog under intratracheal ether anaesthesia. The blood pressure was measured by carotid cannula and mercury manometer. The dose of filtrate corresponded to one-half the transudate from a single strangulated loop. The blood pressure fell from 146 to 30 mm. of

mercury in 40 seconds, and death followed in two and a half minutes (Fig. 18, p. 134).

(2) 1 cc. of protein-free filtrate gave on intravenous injection in the etherised dog a fall in blood pressure from 190 to 119 mm. of mercury, over a period of five minutes. This depression was transient, and the blood pressure quickly resumed its former level (Fig. 19, p.135).

(3) 5 cc. of protein-free filtrate gave on intravenous injection in the etherised dog a fall in blood pressure from 150 to 90 mm. of mercury in three minutes - recovery was slow (Fig. 20, p.135).

(4), (5), (6). In each of these experiments, 3 cc. of the filtrate was injected intravenously in the etherised rabbit, with no effect upon the blood pressure.

(7) A similarly prepared protein-free filtrate of non-toxic transudate from a cat loop strangulated only six hours, had no effect on the blood pressure of the etherised dog.

(8) The rectus abdominis of an adult frog was isolated in a saline bath (content 100 cc.). To the bath was added one hundredth of a gram of eserine sulphate. The addition of as much as 5 cc. of the

protein-free filtrate to the solution in the bath was followed by no contraction of the muscle.

(9) Similarly isolated and eserinated leech muscle also failed to contract when 5 cc. of filtrate was added to the bath.

(10) The addition of 1/5 cc. of the filtrate to a bath in which a strip of virgin guinea pig uterus was suspended from a lever, induced marked contraction of that muscle (Fig. 21, p. 136).

(11) The addition of 1/2 cc. of filtrate greatly augmented the contractions of a strip of cat jejunum, isolated in a 100 cc. saline bath.

(12) The addition of as much as 3 cc. of filtrate to a 100 cc. of saline in a bath in which a strip of rabbit jejunum was suspended, gave no contraction of the isolated gut.

(13), (14). Experiments (10) and (11) were repeated, with the substitution of 1 cc. of protein free filtrate of transudate from a six-hour strangulated cat loop, for the active filtrate from older loops. No contraction followed in either case.

139. Crude Histamine Extract of Transudate
from 24-Hour Strangulated Intestinal
Loops.

To 13 cc. of fresh balloon fluid of established toxicity, drawn from a balloon in which a single loop of cat intestine had been strangulated for 24 hours, alcohol was added to a concentration of 80 per cent., and the mixture was allowed to stand on ice for twenty-four hours. Three volumes of acetone were then added, and the mixture agitated and filtered. The precipitate was dissolved in 20 cc. of saline.

(1) 3 cc. of this extract gave a fall of blood pressure in the etherised dog from 104 mm. of mercury to 55 mm., three minutes after intravenous injection (Fig. 22, p. 138).

(2) 3 cc. of this extract gave a marked fall in blood pressure in the etherised dog (Fig. 23, p. 138).

(3), (4). The injection of 5 cc. of a similar crude histamine extract of the transudate from bowel strangulated only six hours was followed by no alteration in the blood pressure of the etherised dog.

(5) 1/5 cc. of the 24-hour extract, when added to a bath containing 100 cc. of saline, gave marked contraction of the isolated guinea pig uterus (Fig. 26

p. 139), an effect which was not obtained by the addition to the bath of $1/2$ cc. of a similar extract of six-hour balloon fluid.

(6) $1/5$ cc. of the 24-hour extract, added to 100 cc. of saline in which a strip of cat jejunum was isolated, gave marked contraction of this gut. The addition of $1/2$ cc. of a similar extract from a balloon containing a loop strangulated for only six hours, was ineffective (Figs. 24 & 25, p. 140).